Chapter II

RESULTS

Incidence of Poliomyelitis in 1954 Study Areas

Total Incidence - All Ages. The number of cases of poliomyelitis reported in the United States during 1954 was about the same as the average of the previous five years. Since the trial areas were selected largely on the basis of consistently higher case rates during the five year period 1949-53, it is interesting to compare the total reported incidence at all ages in the study areas during 1954 with the previous five year average.

The number of cases reported in 1954 in the study areas was 18 percent below the previous five year average. This reduction was especially marked in placebo control areas where new cases were 27 percent under the 1949-53 average. The decrease in observed control areas was only 12 percent. On the other hand, in non-study areas there was an increase of 4 percent over the five year average. In 1954 about 22 percent of the national case load was reported from field trial areas, the average proportion for 1949-53 was 26 percent.

The incidence of poliomyelitis per 100,000 population was, however, 26 percent higher in all trial areas than in non-trial areas. Attack rates in placebo control areas and in the observed control areas, respectively, exceeded the rate for the rest of the country by 11 percent and 36 percent.

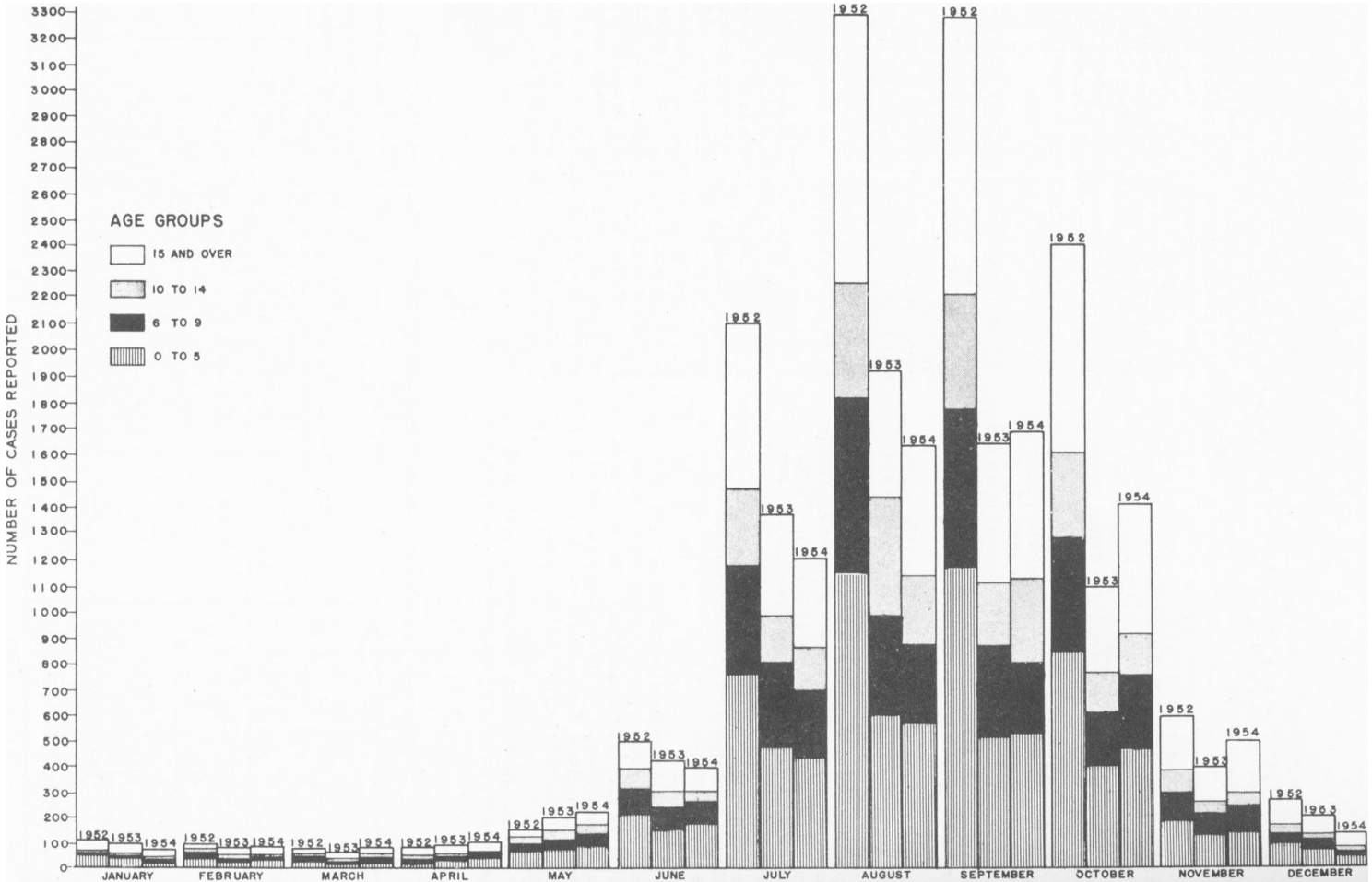
Thus, although the yield of cases in the study areas was not as great as anticipated, it appears that the method of selecting these areas did serve to identify populations with higher poliomyelitis attack rates. It is possible that the adequacy of case reporting in the field trial areas might be greater than in others and there may be additional factors such as variation in diagnostic standards influencing the apparent differences in reported incidence.

The chart on the following page presents the number of cases of poliomyelitis reported by month of onset and age group in the vaccine trial areas for each year, 1952, 1953 and 1954. It illustrates the tremendous variation in incidence from year to year, 1952 being the largest poliomyelitis year on record. But there is no evidence, from inspection, of any marked shift in the age distribution of reported cases.

The percentage distribution of cases in age groups included in the study population is presented later , first for the placebo control areas where attention should be focused on the distribution in the age span six through nine years, and in the observed control areas where the 7-year old children represent most closely the second grade population in which vaccine was utilized. It is evident that in 1954, following the introduction of the vaccination program, there was no observable drop in the percent of total cases included in these age groups. Actually, in observed control areas there was a relative increase in the proportion of 7-year old cases.

Comparative Incidence of Poliomyelitis in Field Trial and Non-Trial Areas, 1954

Area	Reported Cases - All Ages			Case Rate Per 100,000 Population	
	Average 1949-1953	1954	% Change	Average 1949-1953	1954
U.S. Total	39,468	38,768	- 1.8	25.7	24.1
All Study Areas	10,199	8,341	-18.2	33.2	28.9
Placebo Control	4,293	3,133	-27.0	28.9	25.6
Observed Control	5,906	5,208	-11.8	37.3	31.3
Non-Study Areas	29,269	30,427	+ 4.0	23.9	23.0



NUMBER OF REPORTED CASES OF POLIOMYELITIS BY SPECIFIC AGE GROUPS IN THE VACCINE TRIAL AREAS FOR 1952, 1953, AND 1954

Percentage Distribution of Reported Cases of Poliomyelitis in Study Areas by Ages Six Through Nine Years June 15 - December 31, 1952, 1953 and 1954

Age in Years	Percent of Total 1952	1953	1954
Placebo Control Areas			
6	6.5	7.3	6.5
7	4.3	6.2	6.3
8	5.2	4.5	5.3
9	4.0	4.3	3.3
6-9	20.0	22.3	21.4
Total number cases - all ages	4192	3006	2788
Observed Control Areas			
6	6.0	7.6	6.5
7	5.1	5.1	6.8
8	4.5	4.4	3.6
9	4.1	4.4	3.3
Total number cases - all ages	7864	3717	4469

There are, of course, marked limitations to the use of these data in an effort to measure the effect of the vaccine.

1. They include all cases in the age group six to nine years, which is not synonymous with the study population, since included are children in non-participating schools, children age six who are in kindergarten and age nine who are in the fourth grade. Furthermore, detailed investigation of each study case often led to modification of the diagnosis so that the final study case population more truly represented poliomyelitis than the group of reported cases. Actually, there were 1656 cases of poliomyelitis reported from the study areas in the six to nine year age group as compared with 1103 reported cases which were finally determined to have occurred in study children. The case rates by age in the study population are presented to allow comparison.

2. Case reporting practices might have differed considerably in 1954 from those in 1952 or 1953, since the existence of the study may have influenced the extent to which poliomyelitis was recognized and later reported through official channels. Furthermore, in the areas where the control population did not receive placebo, bias may have been introduced in reporting cases in either the vaccinated or non-vaccinated study children.

3. There has been a considerable age shift in the population during the period 1952 to 1954 because of the high birth rates during the post-World War II period. This would tend to lead to an increase in the study population. The extent of this trend cannot be accurately estimated, so that comparisons of age specific rates between years may be in error. The only solid denominator available is the list of children appearing on the Registration Schedules which serves as a basis for determining attack rates in the various components of the study population.

4. The age groups discussed do not fit exactly the grade status of children. Thus, in areas with observed control, the second grade, where all the vaccine was given, is made up roughly, as of clinic time, of 57 percent 7-year olds and 35 percent 8-year olds. The first grade consists of 51 percent 6-year old children and 40 percent 7-year olds. Unfortunately,

Poliomyelitis Morbidity Rates by Specific Years of Age and by Cohort Ages

Vaccine Field Trial Areas
1952, 1953, 1954

Placebo Control Areas

Year	Rate per 100,000 for ages shown 4	5	6	7	8	9
1952	98.9	125.3	148.7	103.6	120.2	85.7
1953		112.0	92.0	101.9	76.0	71.6
1954 Age Group 6 - 9 Years			76.3	74.0	80.7	48.9
Study Population 1, 2, 3 Grades			74.5	65.8	52.7	55.4

Observed Control Areas

Year	Rate per 100,000 for ages shown 4	5	6	7	8	9
1952	153.3	175.0	176.0	156.1	139.6	124.0
1953		84.4	88.5	78.3	63.3	64.5
1954 Age Group 6 - 9 Years			89.5	92.0	64.5	62.2
Study Population 1, 2, 3 Grades			87.5	65.8	52.7	55.4

poliomyelitis attack rates by grade status are not available except in the study areas in 1954.

5. The 1952 epidemic was the largest on record and may very well have behaved differently from the other two years under consideration.

6. In placebo control areas only 56 percent of the study population was inoculated and only half of these received vaccine. In the observed control areas only 65 percent of the second grade children received vaccine.

Information of the actual attack rate based on the age specific population in each of these years is presented on page 17, using as a base population, first the children who were aged six to nine in 1954; these same children would have been five to eight years of age in 1953 and four to seven in 1952.

The second approach uses the base population of six to nine years in each of the years in question. Examination of this material fails to show that the year 1954, when vaccine was utilized, exhibits attack rates in these individual years of age that are different relatively from those in the preceding two years. Obviously, 1952 is a year of high incidence, but a comparison of the years 1953 and 1954 shows the experience of these to be fairly comparable.

Incidence in Study Population. From the total population of 1,829,916, a total of 1103 cases considered to be poliomyelitis was reported to the Vaccine Evaluation Center from May 1 to December 31, 1954. The study period had been defined, however, to start two weeks after the third injections were completed in a given area, corresponding to the time when specimens of serum were obtained for measurement of antibody response. Ninety of the cases, however, occurred during the vaccination period between May 1 and two weeks after the third injections.

They were, therefore, eliminated from consideration in evaluating the effect of the vaccine. Of the remaining 1013 cases, 428 developed among the 749,236 children in placebo control areas; 585 arose in the 1,080,680 children of observed control areas; the corresponding rates are 57 and 54 per 100,000 study population. They constitute the material for analysis.

The curves of incidence and cumulative totals are presented in the appendix.

Study of Possible Reactions to Vaccination

A number of different approaches were made to assess the possible occurrence of reactions following vaccination. These are reviewed here briefly.

1. The study of absenteeism in Pittsburgh schools has already been discussed in a previous section of this summary.

2. Absenteeism in Schenectady, New York. At the suggestion of the Evaluation Center, the New York State Health Department undertook a study of the cause of absences from school among inoculated children during the period of regular field trial clinics in Schenectady, New York. The situation was better suited to study than that in Pittsburgh since placebo was administered to half the children and a properly controlled comparison could be made without knowledge of the inoculum received. The administrative organization for follow-up of the children was somewhat similar to that utilized at Pittsburgh with supervision by physicians in the New York State Health Department. The study was carried out in 24 schools including a total study population of 4,207 children, 1,316 receiving vaccine, 1,304 placebo and 1,587 non-vaccinated.

The extent of absenteeism for each of six weeks after the date of inoculation was identical in vaccinated and placebo populations. Absenteeism in the non-inoculated population did not differ significantly. The listing of 34 causes of absenteeism in the groups as presented in Table XVII (appendix) gives further impressive evidence of the comparability of the populations given vaccine or placebo. The percent of total days of absence attributed to each cause listed does not differ significantly in them. During the 6-week period, there was only one instance of so-called kidney disease, in a child receiving vaccine, that giving rise to a 5-day absence and two leading to a day of absence each in children receiving placebo. Detailed investigation of these illnesses failed to confirm the existence of renal disease in one child and suggested pyelitis in the other two.

Illness labeled "Allergy" caused a total of 66 days of absence, 15 in the vaccinated and 51 in those receiving placebo. In terms of individuals who were ill rather than days of absence the numbers arrange themselves as follows:

	Total	Rash	Poison Ivy	Asthma Hay Fever	Other
Vaccinated	17	8	6	2	1
Placebo	27	12	10	4	1
Total	44	20	16	6	2

It was not firmly established that any of these allergic conditions were related to the inoculation since both vaccine and placebo contained small quantities of penicillin and the essential difference between the products was the absence of poliomyelitis virus and kidney protein in the placebo. Some of the skin conditions were defined as urticaria but did not reappear in those given subsequent inoculations with the same material. It will be seen that the children who did not receive inoculations demonstrated nearly twice as many absences, proportionately, due to

allergic conditions as did those receiving vaccine. The data again indicated a lack of significant untoward reaction to the poliomyelitis vaccine used.

3. Investigation in Nassau County and New York City. A somewhat similar but less comprehensive study was carried out in Nassau County, New York on a small scale with essentially similar findings. Follow-up of possible reactions to inoculation was conducted also by the New York City Health Department. It consisted of investigation of all complaints of reaction that came to the attention of that department during the period after clinics were held and takes the form of merely classifying the causes of complaint following each of the three clinic sessions. The data served merely to illustrate that the number of such complaints was small and that the public was less apprehensive after the second and third clinics than after the first. The illnesses giving rise to these complaints were not remarkable when reviewed as to diagnosis.

4. "Reactions" as Recorded on the Vaccination Clinic Record. During the course of the administration of vaccine and placebo in the various field trial areas information on illness occurring during the course of the 5-week clinic period was to be recorded on the vaccination record filled out for each child at the time. Any serious reaction was to be reported by letter or telephone to the Evaluation Center. There are limitations as to the completeness and accuracy with which these records were prepared. It is assumed, however, that any significant illness would have come to the attention of the clinic physician or those preparing the records. The fact of absence from the clinic was recorded and an entry made as to the reason for absence. These data have been summarized in the following table.

A comparison of the experience in placebo control areas between those receiving vaccine and those receiving placebo is the most informative. Obviously it is difficult or impossible to say with certainty that a given illness is or is not related to vaccination. From a statistical point of view, however, there is some validity in concluding that so-called minor reactions which include fainting, nausea, dizziness, slight rash and cold, occurred with equal frequency in both groups. Common childhood illnesses, mumps, measles, whooping cough, etc. recorded on these records were not tabulated.

The term "major reactions" is inaccurate. It represents major illnesses which might be considered in any way associated with vaccine although usually considered not to be. They were reported on the clinic record because of the urgent request from the Vaccine Evaluation Center that this be done and they include illnesses characterized by the following signs and symptoms; severe rashes, high fevers, severe pains in arms and legs, or any paralysis, major diseases of the nervous system such as encephalitis, meningitis and poliomyelitis, and any diseases of the kidneys. The specific information for each of these cases is presented in the appendix. It is interesting that five of the nine illnesses in the vaccinated group of placebo areas were called kidney disease. This compares with five of the thirteen illnesses in those receiving placebo.

5. In addition to the above specific projects directed towards studying the occurrence of possible reactions in inoculated children a major effort was directed towards uncovering illness in study children during the course of the clinic period and the month following last inoculation through requests for such information addressed to each study area. Local health authorities were urged to telephone the Evaluation Center of the occurrence of untoward reactions in the inoculated group.

A total of 29 reports was received under this system. The cases are roughly categorized as follows: seven reports indicating some form of nephritis or kidney infection, three reported high fevers or encephalitis, fifteen paralysis or muscular weakness, three urticaria, and four some form of anaphylactic shock. The reports indicate no special selectivity in regard to the vaccine, being divided fairly equally between children receiving vaccine and those receiving

Possible Reactions Recorded on Vaccination Record of Inoculated Children

Placebo Control Areas	Population Receiving One or More Injections	Minor Reactions	Major Reactions	Percent Minor	Percent Major
Vaccinated	209,211	931	9	0.4	0.004
Placebo Control	209,806	939	13	0.4	0.006
Observed Control Areas					
Vaccinated	231,902	1,694	7	0.7	0.003

placebo. Those identified as poliomyelitis are discussed in a separate section of the report dealing with the early cases of this disease in the study experience. Those non-poliomyelitis illnesses which were fatal are also discussed later.

Concern with the possibility of transmitting infectious or serum hepatitis when a single syringe was used for the inoculation of five children led several areas to organize their clinics using individual syringes for each child. In order to gain some insight into whether hepatitis was transmitted in this fashion, the New York State Health Department reviewed the reported cases of hepatitis in study children of that state, from areas where the multiple inoculation technic was used. The experience included a total of 36 cases among 71,162 inoculated children and 31 among 49,906 non-inoculated children with rates per 100,000 of 51 and 62 respectively. Study of experience by county and by classroom groupings as well as by time interval after inoculation failed to indicate any significant difference in the hepatitis experience of inoculated and non-inoculated children.

In view of the fact that the vaccine contains minute quantities of kidney protein, concern over safety was expressed by some clinicians before the field trial was initiated. It should be recalled that the minimal requirements for vaccine production devised by Dr. Salk specified that batches of filtered tissue culture fluid with infectious titers of 10^{-5} or greater would be considered suitable for further processing only if they contained less than 0.35 mgm/ml. of total nitrogen, 0.20 mgm/ml. of amino nitrogen and 0.02 mgm/ml. of protein nitrogen. Actually, the nutrient fluid mixture (199) itself (without kidney cells or virus) contains approximately 0.25 mgm/ml. of total nitrogen and 0.12 mgm/ml. of amino nitrogen.

The review above of data collected during the trial bearing on possible reactions in vaccinated children fails to indicate any apparent relationship to kidney disease. There are a few additional data derived from studies of other groups which tend to confirm the lack of any such association. Neva has studied exhaustively the kidney function of 15 vaccinated subjects plus a group of control individuals using daily Addis counts and other test procedures. He failed to find any evidence of kidney damage. Mayer searched for the development of complement fixing antibodies against monkey kidney in a series of paired sera collected pre- and post-vaccination from 100 individuals who had been given multiple doses of vaccine. In only one of these individuals was there any suggestion that such antibodies developed, and this was of doubtful significance. This child had been given vaccine containing adjuvant.

Questions have been raised as to the hazard of inoculating material containing minute quantities of monkey kidney into Rh negative individuals. Dr. Albert Milzer reports that "We were unable to detect Rh and Hr antibodies or sensitization in 32 Rh negative children in our series of immunized children." Dr. A. W. Frisch reports that he was unable to demonstrate Rh antibodies by absorption tests in a group of laboratory workers, inoculated with one of the lots of vaccine used in the field trial. Two of these individuals were Rh negative, but their serums did not show saline, albumin or Coombs antibodies.

Thus, although the data are meager, there is no evidence to date of either kidney damage or Rh sensitization produced by the vaccine.

The Occurrence and Location of Paralysis in Study Population During Vaccination Period and the Subsequent Four Weeks

The preceding discussion emphasized the exacting efforts made to gain information of untoward incidents which might, correctly or not, be considered related to the administration of vaccine. Attention was particularly called to cases of poliomyelitis occuring in the vaccination period and the month after completion of vaccine clinics. It had been suggested that any tendency for vaccine to give rise to cases of poliomyelitis would be most evident in that interval. Moreover, fatalities from any cause were to be carefully investigated.

The first analysis comprised the 90 cases reported during the vaccination period which were excluded from the evaluation. There were, in addition, 39 cases reported in the following two weeks so that between May 1 and four weeks after vaccination 129 cases of presumed poliomyelitis were recorded. These have been examined for location and severity of paralysis with relation to their vaccination status. The results are given in the following table.

There was no instance of involvement of either arm alone or both arms alone, in those receiving inoculations, but there were 4 in uninoculated persons. In the placebo study areas, 8 patients had involvement of arms and legs; in all but three both arms were affected. Three occured in persons who received vaccine, 3 who received placebo and 2 who had no injections. In the observed areas, 24 such instances were reported, 16 had bilateral arm involvement. Five occured in those receiving vaccine, 19 in children who were not inoculated, an equal distribution. See appendix for cases.

Involvement of the legs only was recorded in 3 children receiving vaccine, in 1 with placebo and in 20 who received no injections. There was 1 fatal case of poliomyelitis in a child who had received two injections of vaccine who had a tonsillectomy in the same period; six other cases of poliomyelitis had been reported in the same area. In placebo areas the cases called non-paralytic poliomyelitis or not poliomyelitis were evenly distributed. The observed areas repre-

Vaccination Status	Total Cases	Location of Paralysis														Fatalities		
		Arms Only			Arm and other involvement									Legs Only	None	Polio	Not** Polio	Not*** Polio
					Left			Right			Both							
		L.	R.	Both	Mild	Mod.	Sev.	Mild	Mod.	Sev.	Mild	Mod.	Sev.					
Placebo Areas:																		
Total	32	1	1	-	1	1	-	1	-	-	3	1	1	4	17	1	2	11
Vaccine-Complete	6	-	-	-	-	1	-	-	-	-	1	-	-	-	4	-	-	3
Vaccine-Partial	2	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	1	-
Placebo	7	-	-	-	1	-	-	-	-	-	2	-	-	1	3	-	1	3
No Injection	17	1	1	-	-	-	-	1	-	-	-	1	-	3	9	1	-	5
Observed Areas:																		
Total	97	1	1	-	4	-	1	-	2	1	11	2	3	21	47	3	4	24
Vaccine-Complete	18	-	-	-	-	-	-	-	-	-	2	-	-	4	12	-	2	9
Vaccine-Partial	8	-	-	-	1	-	-	-	-	1*	1	-	-	-	4	1	1	4
No Injection	71	1	1	-	3	-	1	-	2	-	8	2	3	17	31	2	1	11

*This case also had mild involvement in left arm.
**Not included in the total cases.
***Also listed in "Location of Paralysis" section.

sented more Southern states in some of which the incidence of poliomyelitis was already prominent. It appears that reporting of cases of the latter categories were disproportionately common among inoculated children. Of the 86 total cases reported from observed areas by July 1, 35 were from Texas, 7 from Florida, 5 from Oklahoma. The others were scattered through 17 states.

There was in these data, therefore, no evidence of disproportionate frequency of paralytic poliomyelitis in vaccinated or inoculated children up to four weeks after the completion of vaccinations, nor was there any indication of selective localization of paralysis when present.

Measurement of Antigenic Potency of Vaccine

Serologic tests with the sera collected before the first inoculation and approximately two weeks after the third inoculation, as well as from uninoculated children of the observed areas, are not yet completed. Excluding toxic sera, there are now tabulated, however, the results of titrations from nearly 9,000 children in various parts of the United States who received either three doses of one lot of vaccine or specific lot combinations, or who received no vaccine. The distribution is not yet such as to permit mapping of the natural antibody levels for each area adequately. Certain lots of vaccine were used almost entirely in combination with others so that their individual stimulus is not measurable; data concerning at least one other lot are not yet sufficiently reported.

The data have been collected into tables and charts according to lot or lot combinations employed, showing the pre- and post-vaccination titers in parallel with titers of control subjects at the same time. In addition, the responses of those without antibody to any type are grouped. Because the numbers are so uneven at present, strict mathematical evaluation of each lot has not been made. Nevertheless, a grouping of lots has been made according to the response observed and estimated. Five lots and three combinations have been called good; lot 304 appears the best and serves as a standard. Three lots and two combinations are poor, one of them essentially devoid of antigenic activity, as measured, except for a slight effect in persons who already had antibody to Type II or III virus. Two others have little effect for Types I and II but have fair Type III components. The other lots fall in an intermediate position. It is generally true that the Type I component is less effective than the II and III, which tend to be similar although mild variations occur between them.

Classification of Vaccine Lots by their Antigenic Response to Each Polio Type Based on Titer Change Between First and Second Bleedings

Class	Lot No.	Response Type I	Type II	Type III
Good	303	G-	G-	G-
	304	V.G.	V.G.	V.G.
	306	G-	G-	G-
	307	G	G+	G-
	512	G-	G	G
	508-508-309	G	G+	G-
	506-506-309	G	G+	G+
	305-305-307	G-	G	G+

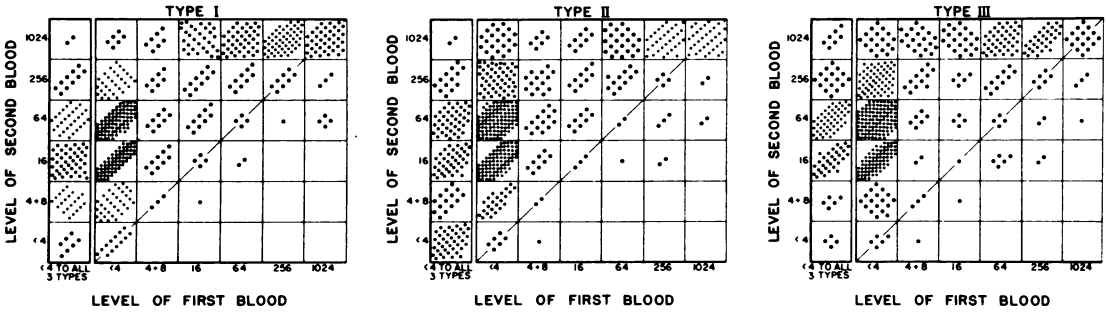
Class	Lot No.	Response Type I	Type II	Type III
Moderate	305	F	G-	G+
	505	F	G	G-
	502-502-307	F	G-	G
	508-508-307	F	G+	F+
	514	F+	G-	G
	506	P	G+	G
Low Moderate	508	F	G-	F+
	506-506-307	F	F+	F
	502-502-309	F	F+	F+
	308	F+	F+	F+
	303-303-307	F+	F+	F+
	502	F	F	F
	513	F	F+	G-
Poor	302	O-T	P	F+
	507	O	O-T	T
	503	O-T	O-T	F
	507-507-307	P	F	F
	507-507-309	P	F	F

V.G. = Very Good
G = Good
F = Fair
P = Poor
T = Trace
O = No Response

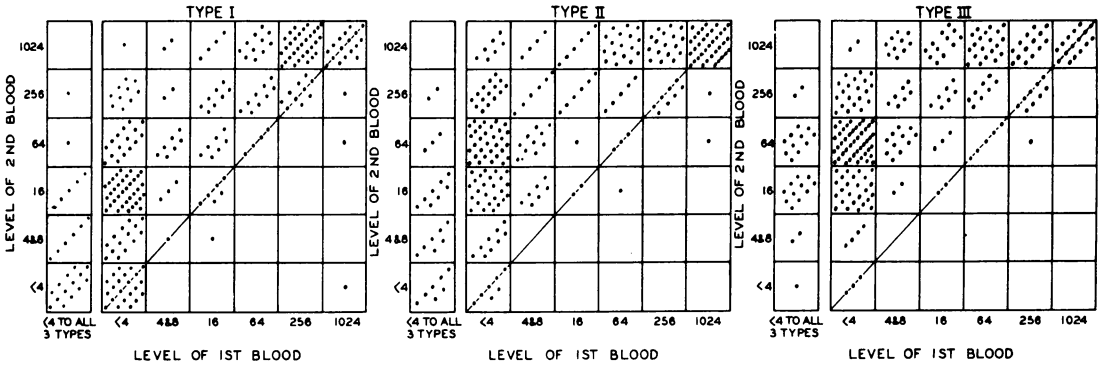
The differences in lots are sharply marked in those without preceding antibody to any type. These persons constituted 21.1 percent of the total, 19.6 percent of those subsequently vaccinated, 22.4 percent of the control group. In the placebo areas 20.6 percent of the vaccinated and 22.9 percent of the placebo controls were in this class.

It is interesting that the variations correspond with the published observations of Dr. Salk from the tests made at the time the lots were examined for release, but generally antigenicity appears somewhat less and in the poor lots, quite sharply less.

SERUM ANTIBODY CHANGES
PRE- AND POST- VACCINATION
VACCINE LOT 304
472 PAIRED SERA



SERUM ANTIBODY CHANGES
PRE- AND POST-VACCINATION
VACCINE LOT 305
225 PAIRED SERA



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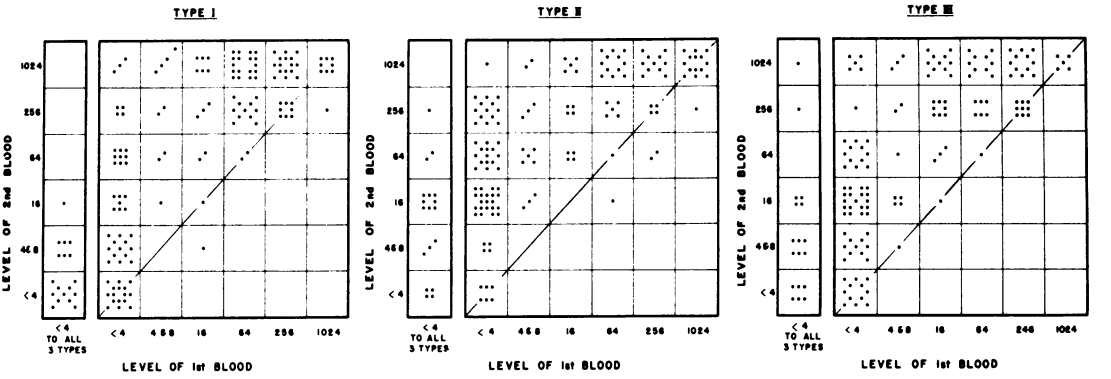
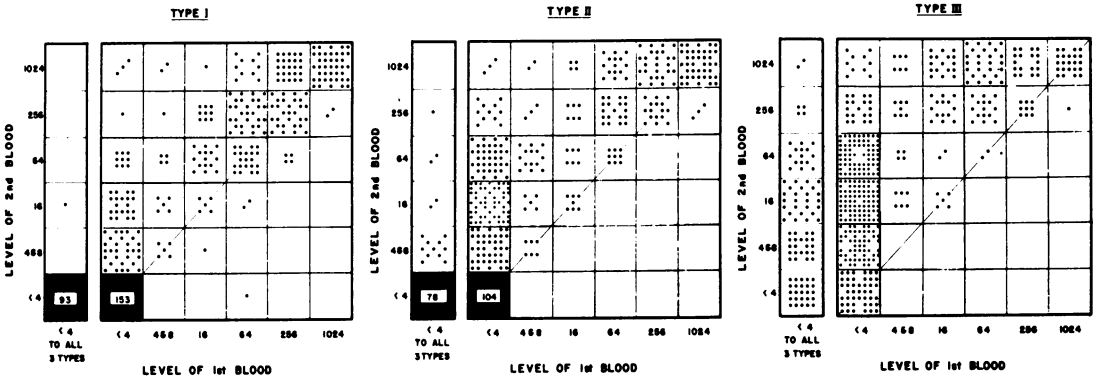
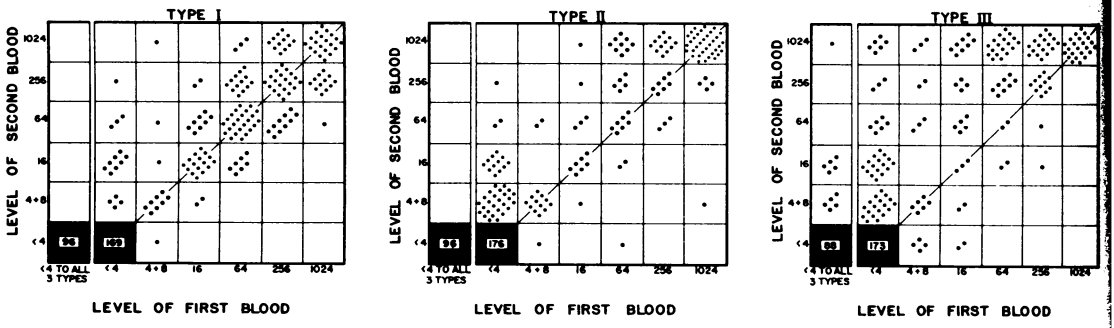
PRE AND POST VACCINATION
VACCINE LOT 508
137 PAIRED SERA



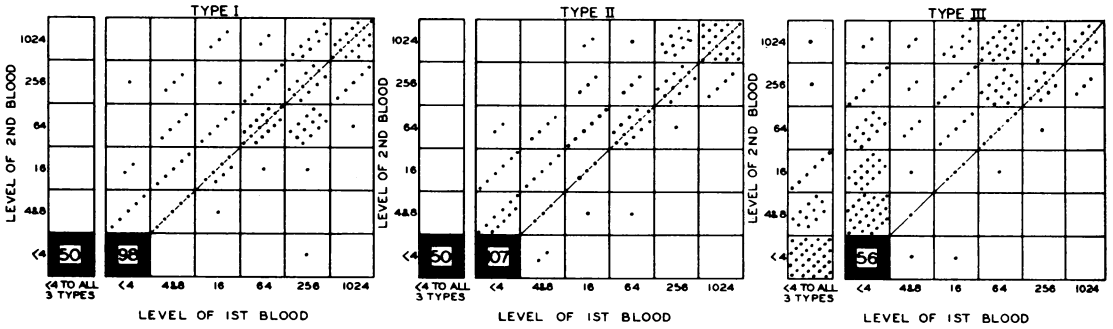
SERUM ANTIBODY CHANGES
PRE AND POST VACCINATION
VACCINE LOT 302
428 PAIRED SERA



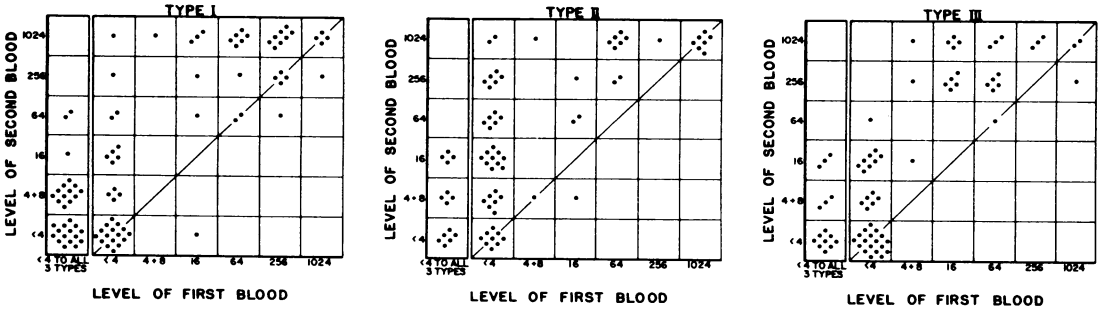
SERUM ANTIBODY CHANGES
PRE- AND POST- VACCINATION
VACCINE LOT 507
347 PAIRED SERA



SERUM ANTIBODY CHANGES
PRE- AND POST-VACCINATION
VACCINE LOT 503
224 PAIRED SERA



SERUM ANTIBODY CHANGES
PRE-AND POST- VACCINATION
VACCINE LOT COMBINATION 507 507 309
63 PAIRED SERA



Persistence of Antibody Response

Data from the third bleedings obtained in November are incomplete and irregularly distributed so that a complete view of the levels of antibody at that time is not available at present. Nevertheless, the accumulated results indicate that when good antibody response resulted from vaccination, the effect was maintained with but moderate decline after five months. There was little suggestion of increases continuing beyond the levels attained two weeks after vaccination, although a few instances of what appeared to be a delayed response were observed. Generally, the decline appeared to be of the order of one dilution so that the number in the highest titer group declined and a greater accumulation appeared in the lowest titer groups. Consequently, when the stimulus was slight, the effect might largely have disappeared in five months But, according to most of the results analyzed, the distribution of antibody levels after five months was still much higher than that in the control population from the same areas, except when poorly antigenic material was involved. Tables of representative data are presented in the appendix.

Distribution of Cases of Poliomyelitis in the Study Groups

General Distribution by Diagnostic Categories: A total of 1013 cases was reported as poliomyelitis during the study period from two weeks after vaccination to December 31, 1954. Of these, 14.8 percent were finally classified as doubtful or not poliomyelitis, 67.6 percent as paralytic poliomyelitis and 17.6 as non-paralytic poliomyelitis. Of those classified as poliomyelitis 79 percent were called paralytic. There is little disparity in the distribution of cases by diagnosis in the placebo and observed study areas. It must be emphasized again that the criteria for the designation "paralytic" were such that patients with minimal involvement are included.

Table 2a. Summary of Study Cases by Diagnostic Class

Diagnostic Class	Total		Placebo Areas		Observed Areas	
	No.	%	No.	%	No.	%
Total	1,013	100.0	428	100.0	585	100.0
Paralytic	685	67.6	270	63.1	415	70.9
Non-paralytic	178	17.6	88	20.5	90	15.4
Doubtful Polio	73	7.2	29	6.8	44	7.5
Not Polio	77	7.6	41	9.6	36	6.2

Distribution by Vaccination Status and Major Diagnostic Classes: In Table 2b the cases are distributed according to the various test and control segments of the study populations and the rates per 100,000 study population in these segments are presented. The evaluation is essentially limited to a comparison of incidence in the vaccinated and in the established controls. In the placebo control areas there is a ratio of 2.5:1 between the total number of cases among those receiving placebo and those given vaccine. When the paralytic cases are considered alone, this ratio becomes 3.5:1. On the other hand, there is no difference in the attack rate of non-paralytic poliomyelitis or in the group called not poliomyelitis in vaccinated compared to control populations.

Table 2b. Summary of Study Cases by Diagnostic Class and Vaccination Status (Rate per 100,000)

Study Group	Study Population	All Reported Cases		Poliomyelitis Cases						Not Polio	
				Total		Paralytic		Non-Paralytic			
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
All Areas - Total	1,829,916	1013	55	863	47	685	37	178	10	150	8
Placebo Areas - Total	749,236	428	57	358	48	270	36	88	12	70	9
Vaccinated	200,745	82	41	57	28	33	16	24	12	25	12
Placebo	201,229	162	81	142	71	115	57	27	13	20	10
Not Inoculated*	338,778	182	54	157	46	121	36	36	11	25	7
Incomplete Vaccinations	8,484	2	24	2	24	1	12	1	12	-	-
Observed Areas - Total	1,080,680	585	54	505	47	415	38	90	8	80	7
Vaccinated	221,998	76	34	56	25	38	17	18	8	20	9
Controls**	725,173	439	61	391	54	330	46	61	8	48	6
2nd Grade Not Inoculated	123,605	66	53	54	44	43	35	11	9	12	10
Incomplete Vaccinations	9,904	4	40	4	40	4	40	-	-	-	-

*Includes 8,577 children who received one or two injections of Placebo.
**First and third grade total population.

In the observed control study, the number of persons in the control population is approximately 3.3 times that of the vaccinated and hence in making comparisons the numbers of cases must be considered in terms of rates. The ratio of total cases in controls to those in vaccinates is 2.2:1 while in paralytic cases this ratio becomes 2.7:1. Here again, however, no difference in attack rates is noted in non-paralytic, or in the not poliomyelitis, doubtful group. The interpretation of the latter observation is not clear from these data, but it should be remembered that the classification of study cases into diagnostic categories was done without knowledge of the patient's vaccination status. There is no evidence of artificial selection suggested.

As indicated earlier, the suggestion was made by certain consultants that a more critical comparison would be achieved in observed control areas, if the attack rate in the total second grade were compared with that in the first and third grades combined. By this procedure the effect of the vaccine used in 65 percent of the second grade population is reduced through the addition of the cases and population among the non-inoculated and partially inoculated second grade population. Despite this redefinition of the test and control groups the differences in poliomyelitis attack rates are highly significant for total cases ($P < .001$) and for paralytic cases alone ($P < .001$).

		Total cases		Paralytic cases	
	Population	No.	Rate per 100,000	No.	Rate per 100,000
2nd Grade	355,507	146	41	85	24
1st & 3rd Grade	725,533	439	61	330	46

The next two tables present the data in greater detail with subdivision of the diagnostic groups and a resultant decrease in numbers of cases per class. Where numbers reasonably permit, estimates of the significance of the differences in rates among vac-

Table 3a. Total Reported Poliomyelitis Cases in Study Population Distributed by VEC Diagnosis, Degree of Paralysis and Vaccination Status—Placebo Areas

VEC Diagnosis by Degree of Paralysis	Number of Cases					Rate per 100,000			
	Total		Vaccinated	Placebo	Not Inoculated	Vaccinated	Placebo	S.L.	Not Inoculated
	No.	%							
Total Cases*	426	100.0	82	162	182	41	81	.001	55
Paralytic Total	269	63.1	33	115	121	16	57	.001	37
Spinal	183	43.0	28	70	85	14	35	.001	26
Score 0	60		9	25	26	4	12	.01	8
1-19	44		9	12	23	4	6	N.S.	7
20-89	47		6	20	21	3	10	.01	6
90-199	23		2	9	12	1	4	.05	4
200+	9		2	4	3	1	2	N.S.	1
Unknown	-		-	-	-	-	-	-	-
Bulbar	14	3.3	3	5	6	1	2	N.S.	2
Bulbo-spinal	68	16.0	2	36	30	1	18	.001	9
Score 0	18		1	10	7	*	5	.01	2
1-19	20		-	13	7	-	6	.001	2
20-89	11		1	5	5	*	2	N.S.	2
90-199	14		-	6	8	-	3	.05	2
200+	5		-	2	3	-	1	N.S.	1
Unknown	-		-	-	-	-	-	-	-
Fatal Polio	4	0.9	-	4	-	-	2	N.S.	-
Non Paralytic	87	20.4	24	27	36	12	13	N.S.	11
Doubtful Polio	29	6.8	13	8	8	6	4	N.S.	2
Not Polio	41	9.6	12	12	17	6	6	N.S.	5

*Excludes two cases who received partial injections.
S.L.—Level of statistical significance.

cinated and controls are attached. The procedure used to estimate the significance of the differences in rates is outlined in the appendix. Table 3a refers to the placebo study areas. Differences at the significance level of .001 (variation this great or greater expected less than once in 1000 similar trials) exist between the rates for vaccinated and control children when viewed as total cases or paralytic, either spinal or bulbo-spinal. Moreover, the differences tend to increase as the severity of disease increases. For example, 33 percent of the spinal paralytic cases in the two lowest grades of paralysis occurred in the vaccinated, but only 23 percent of cases in the three higher grades were vaccinated, and only 2 of the 38 bulbo-spinal cases received vaccine. The four fatal cases of poliomyelitis occurred among children in the placebo control group.

Table 3b presents the same type of analysis of cases in the observed study areas. The significance of differences in rates in vaccinated and control populations in the major categories are also at the .001 significance level. The attack rates for spinal paralytic poliomyelitis were 9 and 27, respectively, in the vaccinated and control groups, and again the difference increased with severity of paralysis. The difference between the attack rates for bulbo-spinal poliomyelitis in vaccinated and controls was significant at .01 but the ratio was only 2:1 as compared with 18:1 in the placebo areas. The difference in cases classified as pure bulbar was, however, more distinct. All eleven fatal cases of poliomyelitis occurred in the control population, a case fatality rate of 2.5 percent for the poliomyelitis cases in the control.

Table 3b. Total Reported Poliomyelitis Cases in Study Population Distributed by VEC Diagnosis, Degree of Paralysis and Vaccination Status—Observed Areas

VEC Diagnosis By Degree of Paralysis	Number of Cases					Rate per 100,000			
	Total		Vaccinated	Control Population	2nd Grade Not Inoc.	Vaccinated	Control Population	S.L.	2nd Grade Not Inoc.
	No.	%							
Total Cases*	581	100.0	76	439	66	34	61	.001	53
Paralytic - total	411	70.7	38	330	43	17	46	.001	35
Spinal	247	42.5	20	199	28	9	27	.001	23
Score 0	79		12	63	4	5	9	N.S.	3
1-19	64		5	51	8	2	7	.01	6
20-89	67		2	53	12	1	7	.001	10
90-199	26		1	22	3	*	3	.05	2
200+	10		-	9	1	-	1	N.S.	1
Unknown	1		-	1	-	-	*	N.S.	-
Bulbar	25	4.3	3	20	2	1	3	N.S.	2
Bulbo-Spinal	128	22.0	15	100	13	7	14	.01	11
Score 0	21		5	14	2	2	2	N.S.	2
1-19	38		6	29	3	3	4	N.S.	2
20-89	33		4	26	3	2	4	N.S.	2
90-199	11		-	9	2	-	1	N.S.	2
200+	23		-	20	3	-	3	.01	2
Unknown	2		-	2	-	-	**	N.S.	-
Fatal Polio	11	1.9	-	11	-	-	2	N.S.	-
Non-Paralytic	90	15.5	18	61	11	8	8	N.S.	9
Doubtful Polio	44	7.6	12	26	6	5	4	N.S.	5
Not Polio	36	6.2	8	22	6	4	3	N.S.	5

*Excludes 4 cases who received partial injections.
**Less than 1 per 100,000.
S.L.—Level of statistical significance.

Table 4a. Distribution of Study Cases by Diagnostic Category, Specimens Examined, Positive Virus Isolation

Diagnostic Category	Total Cases	Placebo Areas			Observed Areas		
		Total Specimens	Virus Isolation		Total Specimens	Virus Isolation	
			Number	Percent		Number	Percent
Total	848	306	170	55.6	416	250	60.1
Paralytic-spinal	434	160	96	60.0	208	125	60.1
Paralytic-bulbo-spinal	197	54	36	66.7	113	81	71.7
Paralytic-bulbar	39	13	9	69.2	19	13	68.4
Non-paralytic	178	79	29	36.7	76	31	40.8

Note: Six fatal cases with isolation omitted.

Frequency of Isolation of Virus in Diagnostic Classes: Stool specimens from 722 of 848 non-fatal cases of poliomyelitis (85 percent) were examined in the laboratories for the presence of poliomyelitis virus. Virus was isolated from 62.1 percent of stools obtained from paralytic cases in the placebo areas and from 64.4 percent of them in observed study areas with a tendency to increased frequency of isolation in the more severe cases. The frequency of virus recovery in the non-paralytic cases was markedly less, 38.7 percent. This raises the question whether it is more difficult to isolate virus from cases of non-paralytic poliomyelitis because they are more resistant or because this diagnostic group includes a significant proportion of cases that are not poliomyelitis. But again it is pointed out that virus was not recovered from 30-40 percent of paralytic cases—Table 4a.

Relation Between Virus Isolation, Serologic Results and Diagnostic Classification: The cases are tabulated in Table 4b on the basis of virus isolation and the associated serologic findings in each clinical category.

There are many features of interest in the data, but the item of immediate concern relates to the serologic findings in patients from whom virus was isolated. Of the paralytic spinal cases with virus isolated and whose sera were studied, 75 percent showed positive or probably positive serologic findings. In the bulbo-spinal cases this was 73 percent and in cases of non-paralytic poliomyelitis it was 68 percent. When attempts to isolate poliomyelitis virus were negative, 44 percent of such cases nevertheless gave serologic results of this same nature. The data bring to the fore the difficult problem of blending the laboratory and clinical data uniformly. Specifically, what bearing should probably positive serologic findings, in the absence of virus isolation, have on diagnosis? The data also present the problem of "other viruses" and their proper position in the field; this will be discussed later.

The Distribution of Laboratory Confirmed Cases According to Vaccination Status: Despite the inability to assess fully the significance of certain relationships observed in the previous table, and the fact that the diagnosis of a number of typical cases of poliomyelitis was not established by laboratory evidence, it was desirable to analyze the distribution of cases, in vaccinated and control groups, that would be fully accepted as confirmed by laboratory findings. Table 5a presents these data for placebo study areas. There were 86 cases, with virus isolated or a 4-fold or greater rise in antibody, in the placebo controls and 18 such cases in the vaccinated; a ratio of approximately 5:1. The numbers in the pure bulbar and fatal groups are small but in all other paralytic classes including those of minimal grade, the differences in the rates between vaccinated and controls were highly significant. On the other hand, the differences in the non-paralytic group were not statistically significant at the .05 level.

As seen in Table 5b much the same pattern exists in observed control areas although, as previously indicated, the difference in the bulbo-spinal class was not as marked as was the case in the placebo study areas.

Table 4b. Diagnostic Classification of Total Study Cases and Results of Laboratory Investigations for Placebo and Observed Areas

Diagnostic Class	Recovery of Virus		Serologic Results				
	Result	No.	Positive	Probable	Indefinite	Negative	None
Total Cases	Total	1013	213	263	282	67	176
	Positive	426	145	130	97	4	50
	Negative	326	53	77	121	41	34
	Other	93	1	26	37	13	16
	Not done	156	14	30	27	9	76
	Detected in family	12	-	-	-	-	-
Paralytic--Spinal	Total	434	111	123	118	3	75
	Positive	221	77	69	47	2	26
	Negative	112	26	33	41	-	12
	Other	35	1	11	16	-	7
	Not done	62	7	10	14	1	30
	Detected in family	4	-	-	-	-	-
Paralytic--Bulbar and Bulbo-spinal	Total	236	70	71	60	5	26
	Positive	139	51	42	33	1	12
	Negative	52	13	12	23	1	3
	Other	8	-	4	2	1	1
	Not done	33	6	13	2	2	10
	Detected in family	4	-	-	-	-	-
Non-paralytic	Total	178	30	53	60	1	33
	Positive	60	17	19	16	1	7
	Negative	69	12	22	27	-	8
	Other	26	-	7	12	-	7
	Not done	22	1	5	5	-	11
	Detected in family	1	-	-	-	-	-
Fatal Polio	Total	15	-	-	1	-	13
	Positive	6	-	-	1	-	5
	Negative	1	-	-	-	-	1
	Other	-	-	-	-	-	-
	Not done	7	-	-	-	-	7
	Detected in family	1	-	-	-	-	-
Doubtful if Polio	Total	73	1	14	33	4	20
	Positive	-	-	-	-	-	-
	Negative	40	1	8	22	2	7
	Other	12	-	4	6	1	1
	Not done	20	-	2	5	1	12
	Detected in family	1	-	-	-	-	-
Not Polio	Total	64	1	-	4	52	6
	Positive	-	-	-	-	-	-
	Negative	43	1	-	4	36	2
	Other	11	-	-	-	11	-
	Not done	9	-	-	-	5	4
	Detected in family	1	-	-	-	-	-
Other Specific Disease	Total	13	-	2	6	2	3
	Positive	-	-	-	-	-	-
	Negative	9	-	2	4	2	1
	Other	1	-	-	1	-	-
	Not done	3	-	-	1	-	2
	Detected in family	-	-	-	-	-	-

Table 5a. Reported Poliomyelitis Cases in the Study Population - Laboratory Positive* Placebo Areas

VEC Diagnosis	Total	Number of Cases			Rate per 100,000			
		Vaccinated	Placebo	Not Inoculated	Vaccinated	Placebo	S.L.	Not Inoculated
Total	198	18	86	94	9	43	.001	28
Non-Paralytic	32	6	11	15	3	5	N.S.	4
Paralytic - Spinal	106	8	45	53	4	22	.001	16
Zero score	21	-	9	12	-	4	.01	4
Scores 1+	85	8	36	41	4	18	.001	12
Paralytic - Bulbar	10	2	4	4	1	2	N.S.	1
Paralytic - Bulbo-Spinal	47	2	23	22	1	11	.001	7
Polio Fatalities	3	-	3	-	-	1	N.S.	-

*Includes 170 cases with poliomyelitis virus isolated
23 no virus but 4-fold or greater rise in antibody in paired sera
5 no virus from patient but poliomyelitis virus recovered from a family member

S.L.—Level of statistical significance.

Table 5b. Reported Poliomyelitis Cases in the Study Population - Laboratory Positive* Observed Areas

VEC Diagnosis	Total	Number of Cases			Rate per 100,000			
		Vaccinated	Control	Not Inoculated	Vaccinated	Control	S.L.	Not Inoculated
Total	300	25	248	27	11	35	.001	22
Non-Paralytic	41	8	31	2	4	4	N.S.	2
Paralytic - Spinal	150	7	127	16	3	18	.001	13
Zero score	36	3	32	1	1	4	.05	1
Scores 1+	114	4	95	15	2	13	.001	12
Paralytic - Bulbar	17	1	15	1	**	2	N.S.	1
Paralytic - Bulbo-Spinal	88	9	71	8	4	10	.01	6
Polio Fatalities	4	-	4	-	-	1	N.S.	-

*Includes 253 cases with poliomyelitis virus isolated
42 no virus but 4-fold or greater rise in antibody in paired sera
5 no virus from patient but poliomyelitis virus recovered from a family member

**Less than 1 per 100,000.

S.L.—Level of statistical significance.

Further examination of the data included consideration of the immunologic type of poliomyelitis virus encountered, together with serologic results. A summary is presented in Tables 6a and 6b.

Of the 315 poliomyelitis viruses isolated and identified from the vaccinated and control subjects, 180 (57 percent) were Type I, 42 (13 percent) were Type II and 93 (30 percent) were Type III. In placebo areas Type I virus was recovered from 39 of the controls and 13 of the vaccinated, a ratio of 3:1. The difference in rates is highly significant statistically. Type II virus was recovered from 6 cases in the controls, but from none in the vaccinated; the small numbers make the results of significance tests questionable. Type III virus was recovered from 25 control patients but from only 2 of the vaccinated, a ratio of 12:1. The significance of this difference again is high. The less pronounced effect in preventing illness due to Type I infection than is true of Type III, may be related to the lesser antigenic effect of the Type I component in the vaccines previously discussed in considering the study of pre- and post-vaccination specimens.

Table 6a. Poliomyelitis Cases in the Study Population by Virus Detection, Serology, Type of Virus, and by Vaccination Status - Placebo Areas

Virus Detection and Serology	Number of Cases			Rate per 100,000			
	Vaccinated	Control Population	Not Inoculated	Vaccinated	Control Population	S.L.	Not Inoculated
Virus Isolation Positive - Total	15	70	85	7	35	.001	24
Serology - Positive and probable	7	43	56	3	21	.001	16
Indefinite	6	13	23	3	6	NS	7
None	2	14	6	1	7	.01	2
Virus Type I - Positive - Total	13	39	49	6	19	.001	14
Serology - Positive and probable	6	27	32	3	13	.001	9
Indefinite	6	8	13	3	4	NS	4
None	1	4	4	*	2	NS	1
Virus Type II - Positive - Total	-	6	9	-	3	.05	3
Serology - Positive and probable	-	4	7	-	2	NS	2
Indefinite	-	-	1	-	-	-	*
None	-	2	1	-	1	NS	*
Virus Type III - Positive - Total	2	25	27	1	12	.001	8
Serology - Positive and probable	1	12	17	*	6	.01	5
Indefinite	-	5	9	-	2	.05	3
None	1	8	1	*	4	.05	*
Virus Isolation Negative - Total	29	31	32	14	15	NS	9
Serology - Positive and probable	8	18	17	4	9	.05	5
Type I	2	9	7	1	4	.05	2
Type II	2	5	4	1	2	NS	1
Type III	4	4	6	2	2	NS	2
Indefinite	16	8	7	8	4	NS	2
None	5	5	8	2	2	NS	2

*Less than 1 per 100,000.
S.L.—Level of statistical significance

Table 6b. Poliomyelitis Cases in the Study Population by Virus Detection, Serology, Type of Virus, and by Vaccination Status - Observed Areas

Virus Detection and Serology	Number of Cases			Rate per 100,000			
	Vaccinated	Control Population	2nd Grade Not Inoculated	Vaccinated	Control Population	S.L.	2nd Grade Not Inoculated
Virus Isolation Positive - Total	20	210	22	9	29	.001	16
Serology - Positive and probable	10	144	15	5	20	.001	11
Indefinite	8	41	6	4	6	NS	4
None	2	25	1	1	3	.05	1
Virus Type I - Positive - Total	14	114	7	6	16	.001	5
Serology - Positive and probable	6	74	6	3	10	.001	4
Indefinite	6	26	-	3	4	NS	-
None	2	14	1	1	2	NS	1
Virus Type II - Positive - Total	2	34	2	1	5	.05	1
Serology - Positive and probable	2	26	2	1	4	.05	1
Indefinite	-	4	-	-	1	NS	-
None	-	4	-	-	1	NS	-
Virus Type III - Positive - Total	4	62	13	2	9	.001	10
Serology - Positive and probable	2	44	7	1	6	.001	5
Indefinite	2	11	6	1	2	NS	4
None	-	7	-	-	1	NS	-
Virus Isolation Negative - Total	39	117	23	18	16	NS	17
Serology - Positive and probable	8	67	9	4	9	.01	7
Type I	4	23	3	2	3	NS	2
Type II	3	16	2	1	2	NS	1
Type III	1	28	4	*	4	.01	3
Indefinite	29	41	12	13	6	NS	9
None	2	9	2	1	1	NS	1

*Less than 1 per 100,000.
S.L.—Level of statistical significance.

In observed study areas the rate of incidence for Type I virus infections with isolation is the same (6 per 100,000) as in the placebo areas but the difference between vaccinated and controls is somewhat less. The rates are much higher than those for Type II and III infections with virus isolation. The differences in rates between vaccinated and control populations for Type II and Type III cases are less striking than in placebo areas, but are still highly significant. Even among the cases classified by type serologically, but without virus isolation, there is a difference in the rates in vaccinated and control populations, significant at the .01 level.

It is noteworthy that the instances of virus isolation from patients with "indefinite" serology tend to be disproportionately common in the vaccinated individuals. Since a large proportion of vaccinated persons may have antibody to the three types of virus this could be expected; hence, the recovery of virus indicates that vaccination and the production of antibodies may not uniformly prevent infection. On the other hand, 67 percent of paralytic cases from whom virus is isolated have antibody to that virus only and in this group are 78 percent of the serological positives and all the probables. Since the percentage of persons in the total sample population bled prior to vaccination and found to have no antibody to any of the three types of poliomyelitis virus is only 20 percent, it follows that 67 percent of the paralytic cases developed in that segment of the population. Of the cases with virus isolated, which occurred in vaccinated children, 31 percent had homologous antibody only. Therefore, these must be patients who had failed to develop antibody from vaccination. This entire phase of the problem requires further study.

The Distribution of Paralytic Cases in Vaccinated and Control Populations According to Lot of Vaccine Used

Further breakdown of the data to consider the efficacy of different lots of vaccine with respect to the different immunologic types of virus is confronted by the limitations of small numbers. Nevertheless, the paralytic cases grouped according to the type of poliomyelitis virus isolated or serologically identified, were tabulated by lot of vaccine concerned. The control subjects were those specifically associated with that lot or lot combination. The numbers include persons from all parts of the country in which the particular lot or combination was employed. There is, of course, great variation in the risk of exposure to poliomyelitis represented by the segments from different areas. Moreover, the prevalence of different types of virus varied geographically. In certain areas most of the cases were caused by Type III virus (Jefferson County, Kentucky, or Utah). In other areas most cases were associated with Type I virus. In no one area was a major prevalence of Type II virus noted.

Placebo Areas: In the placebo study population there were 148 paralytic cases; in 87 of these poliomyelitis virus was recovered; fifty-one Type I, five Type II and thirty-one Type III. Nine or 17.6 percent of the fifty-one Type I cases occurred in vaccinated persons and 42 in the controls, with corresponding rates of 4 and 21 per 100,000. All Type II cases occurred in controls. Three Type III cases occurred in vaccinated children, 28 in the controls. These differences are quite distinct. However, 21 of the paralytic cases, without virus recovered, were in the vaccinates and 40 in the controls, a 1:2 ratio.

The data divided by individual lots are presented in Table VII of the appendix. The lots are also grouped according to the antigenic response previously presented. Among the 84,571 children vaccinated with lots classified as good, two Type I cases and no others occurred, while twenty-six Type I, three Type II and seven Type III cases occurred in the equally numbered controls. There is little doubt of the efficacy of the vaccine in this series and the specific rates for the population concerned emphasize the fact. There was, however, no difference between paralytic cases from whom virus was not recovered.

Approximately 74,000 children received lots characterized as moderate or low moderate. There were three Type I and two Type III paralytic cases among persons receiving these vaccines, with twelve Type I and four Type III cases in the control group. The difference in Type I incidence is significant. About one-third of the cases without virus isolation appeared in the vaccinated children.

The lots designated poor had exhibited very little antigenic potency against Type I, a slight effect for Type II, but the Type III component was fairly good. Among the 42,000 children receiving these two vaccines, there were 4 cases of Type I disease and the same number in the controls, but there were 17 cases of Type III in the controls and only one in the vaccinated. The one lot, 302, was used in Utah where Type III was the prevalent disease, a fortunate circumstance. The most distinct difference in cases from whom virus was not isolated was observed with this lot.

Thus, while the number of cases is not sufficiently large to permit an adequate evaluation of each lot, trends appear to be present which generally are in keeping with the information gained from the serologic studies of pre- and post-vaccination sera. Breaks in vaccinated children were most common with Type I. Protection was most evident when lots of vaccine with good antigen to this type were involved, with rates of 2 in vaccinated and 31 in controls. The poor lots which induced little Type I response gave no evidence of preventing that disease although the Type III effect was distinct. But it must be pointed out that Type I virus infections were half again as common as Type III and the Type II infections were a small minority. The indistinct difference between cases without virus isolation may be the result of a variety of factors.

Observed Areas: In these areas many more combinations of lots were employed although there were several lots which were used alone in relatively large amounts (data presented in table VIII of appendix). But small numbers of cases hinder detailed evaluation of each lot. Because of differences in size of vaccinated and control populations, attention must be directed toward the rates of incidence. In the 50,816 vaccinated with lots considered good antigenically against all three types of virus, no Type I, one Type II and one Type III paralytic cases appeared, with respective rates of 0, 2, 2. In the corresponding controls the respective rates were 14, 4 and 8. The difference between rates in vaccinated and controls is quite definite for Type I and for Type III it is clearly significant. The bulk of the material represents lot 303 and a combination of 305 with 307.

In those receiving the lots graded moderate there were eight cases of Type I paralytic poliomyelitis, no Type II cases and one Type III. Generally, the differences between vaccinated and control in the Type I rates is less distinct than was seen in the good lots but it can be pointed out that in the controls for lots 506 and 508, comprising over 131,000 children there were 30 Type I cases with only one in the 38,000 vaccinated, rates of 23 and 2.6 respectively. In comparison with the single Type III case in vaccinated children there were 37 in the controls. Much of this

Table 7a. Distribution of Study Cases by Antigenicity of Lots of Vaccine and Vaccination Status in Placebo Areas (Rate per 100,000 in study population)

Study Group	Total Cases		Antigenicity Levels Based on Pre- and Post-Vaccination Titers									
			Good		Moderate		Low Moderate		Poor		Mixed Lots	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
Total Reported Cases	428		165		147		28		85		3	
Total Polio Cases	358		135		122		23		76		2	
Vaccinated	57	28	20	24	24	42	1	6	12	28	-	-
Placebo	142	71	62	73	35	62	8	46	37	87	-	-
Non-inoculated	159		53		63		14		27		2	
Paralytic Cases	270		95		92		18		63		2	
Vaccinated	33	16	12	14	13	23	-	-	8	19	-	-
Placebo	115	57	46	54	29	51	7	41	33	78	-	-
Non-inoculated[1/]	122		37		50		11		22		2	
Non-Paralytic Cases	88		40		30		5		13		-	
Vaccinated	24	12	8	9	11	19	1	6	4	9	-	-
Placebo	27	13	16	19	6	11	1	6	4	9	-	-
Non-inoculated[1/]	37		16		13		3		5		-	
Not Polio	70		30		25		5		9		1	
Vaccinated	25	12	11	13	8	14	1	6	5	12	-	-
Placebo	20	10	10	12	7	12	-	-	3	7	-	-
Non-inoculated	25		9		10		4		1		1	

[1/]Includes one case with incomplete injections

centered about Louisville, Kentucky, where Type III poliomyelitis was highly epidemic and where lot 506 or 506 combined with 307 was used. The rate in the controls was 18 per 100,000 and 0 in the vaccinated. It is of interest, too, that a distinct difference in distribution of cases without virus isolation occurred in this group as well, 3 in vaccinated, a rate of 6, and 33, a rate of 22, in controls, suggesting that many of them were in fact, Type III infections. There were no cases of Type II in vaccinated and 11 in the controls in the moderate groups.

The lot graded as poor, 507, elicited essentially no antibody to Type I and minimal response to the others. It was given to 21,635 children among whom one Type I, one Type II and two Type III paralytic cases occurred. The rates were 5, 5 and 9, respectively, and in the controls were 12, 14 and 14. There is no significant difference between the rates in these groups. Children vaccinated with this lot were the only group in which cases caused by each of the three types of virus appeared. And, although the numbers involved do not permit a precise conclusion statistically, the lack of significant difference in rates, the knowledge of its antigenic impotence and the distribution of cases combine to indicate that it was an ineffective vaccine. An additional 18,545 children were given this lot for the first two doses and a different one for the third. Among them no paralytic cases due to a typed virus occurred, while in the controls there were thirteen Type I, one Type II, and five Type III cases. Here, too, the difference between untyped cases appeared distinct.

The discussion has given emphasis to the fact that the relatively small size of the populations involved, the differences in distribution of infecting types, and the irregularities of prevalence contribute restrictions to detailed analysis. It is evident that the results obtained represent the influence of a number of vaccines and the summary data are a composite of those effects.

Table 7b. Distribution of Study Cases by Antigenicity of Lots of Vaccine and Vaccination Status in Observed Areas (Rate per 100,000 in study population)

Study Group	Total Cases		Antigenicity Levels Based on Pre- and Post-Vaccination Titers									
			Good		Moderate		Low Moderate		Poor		Mixed Lots	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
Total Reported Cases	585		103		122		178		144		38	
Total Polio Cases	505		90		103		158		119		35	
Vaccinated	56	25	7	14	12	27	16	23	17	37	4	35
Controls	391	54	72	42	80	54	123	53	90	63	26	76
Non-inoculated	58		11		11		19		12		5	
Paralytic Cases	415		81		85		132		88		29	
Vaccinated	38	17	5	10	9	20	11	16	10	22	3	26
Controls	330	46	67	39	67	45	106	46	68	48	22	64
Non-inoculated[1/]	47		9		9		15		10		4	
Non-Paralytic Cases	90		9		18		26		31		6	
Vaccinated	18	8	2	4	3	7	5	7	7	15	1	9
Controls	61	8	5	3	13	9	17	7	22	16	4	12
Non-inoculated	11		2		2		4		2		1	
Not Polio	80		13		19		20		25		3	
Vaccinated	20	9	1	2	7	16	4	6	5	11	3	26
Controls	48	7	10	6	8	5	13	6	17	12	-	-
Non-inoculated	12		2		4		3		3		-	

[1/]Includes four cases with incomplete injections

Further Consideration of Paralytic Cases in Vaccinated Persons

Of the 84 cases reported as poliomyelitis in vaccinated children of the placebo study areas, there were 34 classified as paralytic poliomyelitis of all grades. They are divided as follows according to the results of stool examination for virus. There were 10 from whom Type I virus was recovered and one Type III virus. But, in addition, there are 5 unidentified or "orphan" viruses all recovered from patients in Massachusetts and central New York State. The three in which serologic studies were done presented no evidence of poliomyelitis virus infection, in fact, they had antibodies to all three types. These data demonstrate further the need for analysis in which only the "positive" cases of poliomyelitis are included.

From 6 of the 25 non-paralytic cases "orphan" viruses were recovered; 5 of these were also from Massachusetts and central New York. All 5 had antibody to all three types of poliomyelitis virus. The other case had only a high antibody level to Type I virus. From 5 of the remaining non-paralytic cases Type I virus was recovered.

Paralytic cases	Tot.	Poliomyelitis virus			Unidentified "orphan" virus	Other specific virus	No virus	Not done
		I	II	III				
Spinal	29	7*	-	-	5	-	13	4
Bulbar and bulbospinal	5	3	-	1	-	-	1	-

*Includes one patient with incomplete vaccination.

Of the 10 paralytic cases from whom Type I virus was isolated, 6 came from New York State. In only one, possibly two, of the 8 tested was antibody to all three types of virus present indicating the lack of a full vaccination effect and also suggesting that they had not previously developed Type I

antibodies. The patient with Type III virus infection exhibited antibody to only that type. There is a further suggestion that antibody to heterologous types was also developing in certain cases although they were not close to the time of vaccination. Three had, in addition, significant rises to the homologous virus. It is of interest that in those with negative stools among the vaccinated there were 7 who had antibody to a single type of virus indicating the lack of full vaccine effect.

In the observed areas there were ten Type I, two Type II and four Type III viruses isolated from the paralytic cases occurring in vaccinated children.

Paralytic cases	Tot.	Poliomyelitis virus I	II	III	Unidentified "orphan" virus	Other specific virus	No virus	Not done
Spinal	23	4*	2	-	3	-	13**	1
Bulbar and bulbospinal	19	6	-	4	-	-	8*	1

*Includes one patient with incomplete vaccination.
**Includes two patients with incomplete vaccination.

Eight of the 15 had antibody to only one type of virus, 4 exhibited good levels to all types, 2 of whom had quite definite paralysis. The others had antibody to two types at low levels. There was also a Type I isolated from a patient with incomplete vaccination. Including the 5 cases of non-paralytic poliomyelitis from whom Type I virus was isolated, 10 of the 21 total cases had antibody only to the homologous type, suggesting failure of antigenic response to the vaccine used. The 4 cases developing in persons vaccinated with Lot 507 had antibody derived only from the infecting virus, whether Type I, II or III, again emphasizing its lack of antigenic effect.

Orphan viruses were recovered from 3 of the cases classified as paralytic, these from widely separate parts of the country.

This brief survey points out that 11 of 36 cases in vaccinated children from whom poliomyelitis virus was recovered, possessed antibody to only one type of virus, even in convalescence. This indicates rather precisely that a significant number of the patients who developed poliomyelitis, despite vaccination, had failed to develop antibodies as a result of vaccination. In some instances the failure was related to the lot of vaccine used but in others there must have been variations of another kind which were responsible.

The Relation Between Original Reported Diagnosis and Final Classification of Cases in Study Population

In Tables 8a and 8b information is presented to show the final classification of cases reported to the Evaluation Center in comparison with the diagnosis indicated on the Clinical Epidemiological record. It is apparent that the major change occurs in those with an original diagnosis of non-paralytic poliomyelitis. In both placebo and observed study areas approximately half of them (52 percent) were moved into a paralytic category. This illustrates the fact that the detailed muscle examination detects muscular impairment which might be overlooked readily and further, that the final diagnostic category "minimal paralytic" conservatively avoids exclusion of patients about which doubt might well exist as to the presence of paralysis.

Approximately 30 percent in placebo areas and 27 percent in observed areas remained in the non-paralytic class while the remainder were considered not poliomyelitis or doubtful.

A Comparison of the Distribution in Vaccinated and Controls of Paralytic Cases According to Degree of Muscular Impairment Measured at First and Second Examination

The results of the physical therapists' examination made 50-70 days after onset were compared with those of examinations of the same patients made 10-20 days after onset, all of whom were classified by the Vaccine Evaluation Center as paralytic. The groups in grade I without scores are presented separately from those with score and the grade II group (score 1-19) are also listed separately from those with higher grades of involvement.

In placebo control areas, Table 9a, the ratio of total cases, occurring in placebo controls to those in vaccinated is 3.5:1 when either the first or second muscle grading is used as a basis for classification. In the group I spinal (zero score) the ratio is 3:1 based on the first examination and 1.8:1 on the second examination. This would suggest either that vaccine failed to prevent these cases or that a fair proportion of illnesses, so classified, were not poliomyelitis. Within the limits of the small numbers, the ratio of cases in placebo controls to those vaccinated was sharply increased in cases classified as bulbo-spinal, even when the score was zero (17:1). In spinal paralytic poliomyelitis with a score these ratios clearly demonstrated the protective effect of vaccine.

Comparison between the protective effect demonstrated in cases classified by the findings of

Table 8a. Distribution of Study Cases by Final Diagnosis Determined at Evaluation Center Compared with Initial Diagnosis Made in Field and Reported on Form FT-6—Placebo Areas

Diagnosis as Reported on FT-6	Final Diagnosis as Determined at Evaluation Center							
	Total Cases	Non-Paralytic	Paralytic				Doubtful Polio	Not Polio
			Spinal	Bulbar	Bulbo-Spinal	Polio Fatality		
Total Cases	428	88	184	14	68	4	29	41
Non-paralytic	231	71	99	6	10	-	21	24
Paralytic:								
Spinal	83	4	62	2	10	-	1	4
Bulbar	38	-	2	6	26	4	-	-
Bulbo-spinal	21	1	4	-	15	-	-	1
Encephalitic	1	1	-	-	-	-	-	-
Not specified	27	4	14	-	6	-	1	2
Suspect:								
Paralytic	1	-	-	-	-	-	-	1
Not specified	18	6	2	-	-	-	5	5
Not classified	2	-	1	-	1	-	-	-
Not Polio	6	1	-	-	-	-	1	4

Table 8b. Distribution of Study Cases by Final Diagnosis Determined at Evaluation Center Compared with Initial Diagnosis Made in Field and Reported on Form FT-6—Observed Areas

Diagnosis as Reported on FT-6	Final Diagnosis as Determined at Evaluation Center							
	Total Cases	Non-Paralytic	Paralytic				Doubtful Polio	Not Polio
			Spinal	Bulbar	Bulbo-Spinal	Polio Fatality		
Total Cases	585	90	250	25	129	11	44	36
Non-paralytic	281	77	119	10	20	-	32	23
Paralytic:								
Spinal	134	6	90	3	27	-	4	4
Bulbar	67	1	3	11	46	6	-	-
Bulbo-spinal	35	-	3	1	23	5	2	1
Encephalitic	5	-	2	-	2	-	1	-
Not specified	36	2	25	-	9	-	-	-
Suspect:								
Paralytic	-	-	-	-	-	-	-	-
Not specified	17	2	5	-	2	-	5	3
Not classified	4	-	3	-	-	-	-	1
Not Polio	6	2	-	-	-	-	-	4

Table 9a. Vaccination Status of Paralytic Spinal and Bulbo-spinal Study Cases Classified by Extent of Paralysis as Measured by Both the 10-20 Day and 50-70 Day Muscle Examinations - Placebo Areas

Vaccination Status	Type and Extent of Muscular Involvement													
	Based on 10-20 Day Muscle Examination							Based on 50-70 Day Muscle Examination						
	Total	Total Excluding Spinal Zero Score	Spinal Zero Score	Bulbo-spinal Zero Score	Combined Spinal and Bulbo-spinal with Score			Total	Total Excluding Spinal Zero Score	Spinal Zero Score	Bulbo-spinal Zero Score	Combined Spinal and Bulbo-spinal with Score		
					1-19	20+	Unk.					1-19	20+	Unk.
Total	251	193	58*	15	57	101	20	251	159	92	31	49	77	2
Vaccinated	30	22	8	1	8	11	2	30	12	18	1	5	6	-
Placebo	106	82	24	8	22	44	8	106	73	33	17	23	31	2
Not Inoculated	115	89	26	6	27	46	10	115	74	41	13	21	40	-
Ratio Placebo Cases Vaccine	3.5	3.7	3.0	8.0	2.7	4.0	4.0	3.5	6.1	1.8	17.0	4.6	5.2	-

* One additional case had spinal paralytic polio with zero score on both examinations but who received only two inoculations of vaccine.

Table 9b. Vaccination Status of Paralytic Spinal and Bulbo-spinal Study Cases Classified by Extent of Paralysis as Measured by Both the 10-20 Day and 50-70 Day Muscle Examinations - Observed Areas

Vaccination Status	Type and Extent of Muscular Involvement													
	Based on 10-20 Day Muscle Examination							Based on 50-70 Day Muscle Examination						
	Total	Total Excluding Spinal Zero Score	Spinal Zero Score	Bulbo-spinal Zero Score	Combined Spinal and Bulbo-spinal with Score			Total	Total Excluding Spinal Zero Score	Spinal Zero Score	Bulbo-spinal Zero Score	Combined Spinal and Bulbo-spinal with Score		
					1-19	20+	Unk.					1-19	20+	Unk.
Total*	375	301	74	19	83	165	34	375	247	128	59	74	111	3
Vaccinated	35	23	12	5	10	6	2	35	17	18	8	6	3	-
Control	299	240	59	13	64	137	26	299	200	99	43	64	90	3
2nd Grade Not Inoculated	41	38	3	1	9	22	6	41	30	11	8	4	18	-
Vaccinated x factor**	115	76	39	16	33	20	7	115	56	59	26	20	10	-
Ratio Control Cases Vaccine	2.6	3.2	1.5	0.8	1.9	6.9	3.7	2.6	3.6	1.7	1.7	3.2	9.0	3/0

* Four paralytic cases with zero score on second examination were incompletely vaccinated and are not shown in this table.

** Since control population in 1st and 3rd grades was 3.28 times as large as the population of completely vaccinated children, the number of cases in vaccinates is multiplied by this factor in order to put them on a comparable population base.

the first examination with that based on the second, or 50-70 day, examination indicates that use of the residual paralysis as a measure of severity tends to accentuate the difference in the poliomyelitis attack rate between vaccinated and control individuals. This, with most of the other data presented previously, indicates that the frequency of severe paralysis is less common in the vaccinated group.

The improvement occurring in the interval of two months, tends to reduce the number of cases with well marked impairment. This trend might suggest that loss of demonstrable impairment has occurred in a larger proportion of the vaccinated than in those cases receiving placebo.

It may merely mean, however, that as the complicating pain and spasm of the earlier stage of illness disappears, a larger proportion of cases with significant earlier scores now congregate in the zero score category. This shift is most noticeable in the patients with less extensive muscle involvement, those with high scores remaining at that level on both examinations.

In the observed control areas, Table 9b, a similar shift in improvement is noted, but the variation between the findings of the first and second examinations is less marked. In all of these data, however, is the indication that, at any stage, the preventive effect of vaccine is more distinct as the severity of the disease increases.

Distribution of Cases in Study Groups by Age, Sex, and Diagnosis

Reference has been made repeatedly to the complete comparability in all the general characteristics, (i.e. numbers, school, grade, age, sex, race, social economic status, antibody levels, etc.) of the populations receiving vaccine and placebo.

There has been complete acceptance of the fact that the comparison between these groups represents the actual control study and that the uninoculated population cannot be considered an additional control. Nevertheless, so that any desired comparisons may be made, the number of cases in uninoculated persons has been included in most of the tables without further discussion, although there are many interesting facets for subsequent consideration. One may, in general, say that the non-inoculated second graders of the observed areas and the uninoculated part of the placebo areas have a frequency of involvement which lies between the vaccinated and established controls. This was anticipated from differences in their characteristics demonstrated by survey.

The same applies to the observed control study areas where many will be tempted to make aggregations other than those established for the study. These data have been presented in a number of places in the report so that those who desire may do so.

The comparability of the vaccinated and placebo control populations in the placebo study areas provided data, therefore, for consideration of the effect of vaccine on an age-specific basis.

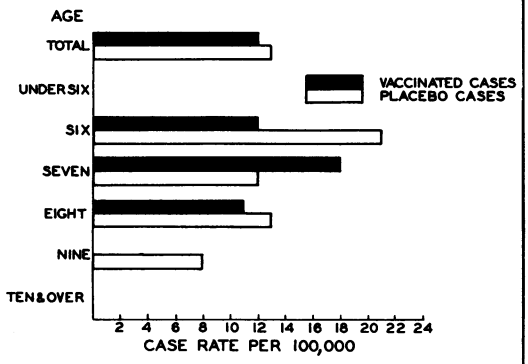
The detailed data on the number of cases and the attack rates by clinical classification and year of age for vaccinated and control populations in both the placebo control and observed control areas are presented in the appendix. The essential findings, illustrated in the following charts, serve to confirm for both types of study on an age specific basis, the conclusions already reached in the preceding discussion; namely, that against paralytic poliomyelitis, vaccination had a preventive effect. With illness classified as non-paralytic poliomyelitis, no effect was observed.

The protective effect with respect to paralytic poliomyelitis is significant for each year of age except in the 6 year olds, where based on 16 and 23 paralytic cases, the attack rates are 37 and 53 per 100,000 population in vaccinated and placebo controls respectively. The comparable rates for the 7 year old children were 16 and 69 per 100,000 and for the 8 year olds, 7 and 53 per 100,000 for the test and control groups respectively. The apparently high rate in placebo control children under 6 years of age is fictitious, since it is based on a single case in this group compared with no cases in the small group of vaccinated children in this age group. Thus there appears to be progressive increase in the protective effect as age increases. Since the difference in attack rate between vaccinated and control 6 year olds is not statistically significant a question might be raised as to how and why this group differed from the older children.

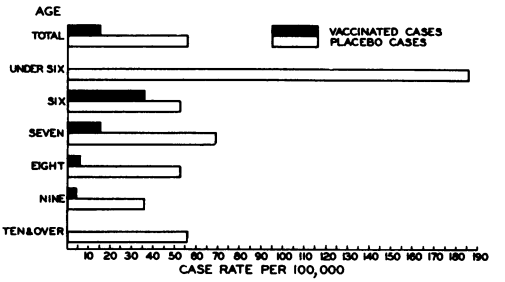
A review of the results of serologic study of pre- and post-vaccination sera from 6 year old children in placebo control areas indicates that these children do not differ strikingly from 7 or 8 year olds. Of 292 six year old vaccinated children studied from these areas, 69 or 23.6 percent had no antibodies to any type in the prevaccinal blood sample. For the 7 year olds the figures are 150 of 649 or 23.2%; the 8 year olds 124 of 644 or 19.3% and the 9 year olds 58 of 328 or 17.7%. The proportion of the pre-vaccine sera from children given placebo that showed no antibodies to any type were 27.5%, 25.4%, 22.6% and 17.5% for these same years of age. Thus, the initial proportion of children without antibody did not differ strikingly, at least in the 6 and 7 year old children.

The antigenic response exhibited by 6 year old children following vaccination, likewise, did not differ from that of the 7 year olds, as indicated by the following table:

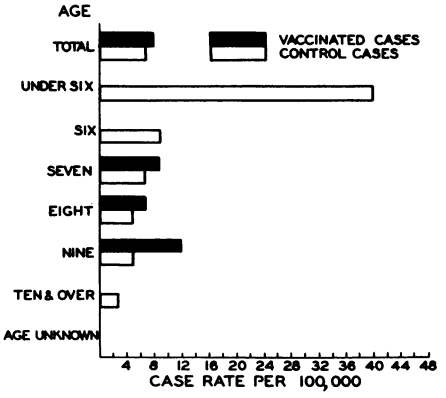
INCIDENCE RATES FOR NON-PARALYTIC CASES BY AGE AND BY VACCINATION STATUS- PLACEBO AREAS



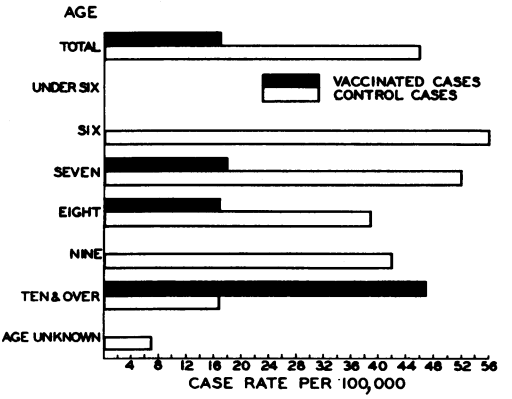
INCIDENCE RATES FOR PARALYTIC CASES BY AGE AND BY VACCINATION STATUS - PLACEBO AREAS



INCIDENCE RATES FOR NON-PARALYTIC CASES BY AGE AND BY VACCINATION STATUS-OBSERVED AREAS



INCIDENCE RATES FOR PARALYTIC CASES BY AGE AND BY VACCINATION STATUS -OBSERVED AREAS



Titer of Type specific antibody in post-vaccination sera from 6 and 7 year old children who had no antibody to any type before vaccination

Placebo Control Areas

Age	Total Sera	Type	Percent having indicated antibody in post-vaccination serum					
			<4	4-8	16	64	256	1024
6 Yrs.	72	I	47	18	18	7	3	7
		II	36	7	25	19	10	3
		III	32	12	21	26	6	5
7 Yrs.	152	I	45	14	23	11	4	3
		II	41	9	22	18	7	3
		III	20	17	25	23	9	5

Thus, the 6 and 7 year old children did not differ significantly, on the basis of serologic evidence. A review of the clinical and laboratory evidence upon which diagnosis was based in these 6 year old cases does not show them to differ from cases in other study children. Their distribution by extent of muscle involvement was as follows:

	Paralytic						
	Zero	1-19	20+	Bulbar and bulbo-spinal	Deaths	Non-Paralytic	Not Polio
Vaccine	4	6	4	2	0	5	3
Placebo	6	3	2	11	1	9	4

When attention is directed toward cases in this age in which poliomyelitis virus was isolated the following distribution is observed:

	Paralytic			Non-Paralytic		
	Type of Virus			Type of Virus		
	I	II	III	I	II	III
Vaccine	4	0	0	0	0	0
Placebo	4	1	5	2	0	0

The data available are inadequate to allow further speculation as to the protective effect of vaccination in 6-year old children. In observed areas there were only 1963 vaccinated 6-year old children and no cases developed in this group so that this experience is of little value in assessing the problem.

Review of Deaths in the Study Population

Several mechanisms were devised to keep track of the deaths from all causes in members of the study population. Each study area was asked to report weekly to the Evaluation Center deaths from all causes in children aged 6 - 9 years that had occurred during that week. The initial report was to include a cumulative listing of deaths from the beginning of the year through May 1. It was emphasized that deaths from significant causes, where the question of relation of illness to vaccination might arise, be investigated even more thoroughly, with autopsy and expert laboratory assistance. The Evaluation Center was to be informed immediately by telephone so that a team of experts might be brought in, if necessary.

These matters were reemphasized repeatedly throughout the study period and a careful record of all reports from the field was kept. Despite these efforts, however, the reporting of deaths from all causes was inadequate as measured by death rates in this age group for recent years in the United States as a whole. At the end of 1954, systematic efforts were made to have each study area review all deaths which had occurred in the age group 6 - 9 years in the area, in an attempt to identify those in study children. As of the present time, a total of only 440 deaths, occurring during the period May 1 - Dec. 31, 1954 in children of this age group in study areas has been brought to the attention of the Evaluation Center through submission of death certificates or other notification. Essentially all of these deaths are in study children and review of the cause of death indicates that the distribution by cause does not differ significantly from that in the rest of the United States for this same age group.

The proportion of these deaths in the leading categories is presented as follows, with the percent in parenthesis indicating the proportion of deaths in these same diagnostic categories for the age group 5 - 9 years in the United States in 1952.

Accidents	36%	(35%)
Cancer	15%	(12%)
Pneumonia	9%	(6%)
Heart Disease	7%	(4%)
Poliomyelitis	5%	(7%)
Nephritis	2%	(3%)
Congenital Defect	2%	(5%)

The expected total number of deaths in the study population was 706 based on the data for this age group in the United States as a whole. This suggests, that despite the efforts to obtain complete reporting, major deficiencies still exist.

In placebo control areas, where the reporting of deaths to the Evaluation Center could not have been

influenced by knowledge of the vaccination status of the child, there were six deaths due to causes other than poliomyelitis which have some interest because of their involvement of the central nervous system, the kidney or the liver. These are listed below by cause and date of death and type of inoculation.

Cause of Death	Date	Type of Inoculation
1) Uremia, acute nephritis	6/3	Placebo 1 injection
2) Acute encephalitis	5/18	Vaccine 2 injections
3) Meningoencephalitis	5/23	None
4) Meningitis	10/24	None
5) Meningitis	12/ ?	None
6) Acute yellow atrophy of the liver	12/13	Placebo 3 injections

The one death listed above in a vaccinated child from Iowa (No. 1102-01) was considered on the death certificate to have died from chicken pox encephalitis. He received injections of vaccine on 4/30 and 5/7. On 5/10 he developed a rash characteristic of chicken pox. He became lethargic on 5/13 improved temporarily only to start vomiting and became comatose on 5/17 the day before death. Lumbar puncture showed only 3 WBC per cu. mm. in the spinal fluid. Autopsy performed after embalming, revealed evidense of hepatitis and terminal hemorrhagic pneumonia. Histologic examination of the central nervous system showed no abnormality. Brain, lung, liver and other tissue specimens removed at that time, but unfortunately placed temporarily in formalin, were submitted to the University of Kansas Medical Center for attempts to isolate virus. Suspensions of 14 such specimens were tested for virus in monkey kidney tissue culture. No virus was recovered. Certainly the etiology of this bizarre illness is not clear. It would seem likely that the relationship to vaccination is merely coincidental.

The death (No. 4102-02) from acute nephritis in a child who received a single injection of placebo on 4/27 was preceded by an upper respiratory infection which had onset 4/19 and which was treated with one injection of penicillin. On 5/3 the child developed edema of the face and general anasarca with marked hematuria and uremia. She became progressively worse and died on 6/3. Autopsy confirmed the presence of nephritis. Blood obtained postmortem contained no antibodies to any type of poliomyelitis.

In observed control areas, a similar review of deaths in study children was undertaken. In no instance was evidence uncovered of clear cut association with vaccination. All these deaths seemed to be explained adequately on other grounds. Presented below are brief summaries of the clinical and pathological findings in these cases.

1. Case 0403-24 from Denver, Colorado while vacationing in the mountains became ill with fever and headache 5 days after receiving her third dose of vaccine (Lot 303). That evening she became comatose and was dead on arrival at the hospital. Autopsy demonstrated the existence of congenital heart disease (patent ductus arteriosus and patent foramen ovale), with hypertrophy of the right chambers of the heart and hemorrhagic pulmonary edema as sequelae. Coccidioidomycosis of the lower lobe of the right lung was also found. Gross and microscopic examination of the central nervous system showed no abnormality. It seems likely that the child died of acute heart failure, possibly secondary to her activities while on vacation at a high altitude.

2. Case 1006-05 from South Bend, Indiana became ill on 6/22, eighteen days after receiving her third inoculation of vaccine (Lot 305 and 307). The child gave a history of prior kidney infection. The course was rapidly down hill with persistent vomiting, abdominal pain, ascites, uremia and respiratory failure. Post mortem examination demonstrated the presence of acute pyelonephritis, staphylococcal septicemia, secondary to this bronchopneumonia, and ascites. Gross and microscopic examination of the central nervous system showed no abnormalities suggestive of poliomyelitis. No virus was recovered from the stool and portions of the brain and cord.

3. Case 1801-04 from Jackson, Mississippi developed severe headache and projectile vomiting on 5/29. He had received two inoculations of vaccine (Lot 305) on 4/28 and 5/5. He progressed downhill rapidly with frequent convulsions and died on 5/30. Lumbar puncture demonstrated spinal fluid containing 146 white cells/cu. mm. The history of the child indicated that in June 1953 he fractured two cervical vertebrae. He was put in traction for many months and the neck brace was not removed until May 1954 shortly before the final illness. Apparently there had been complete healing of the bone, without neurologic, muscular or bony defects. Autopsy revealed cerebral edema, focal, acute subarachnoid hemorrhage, over the pons and medulla and focal meningitis. No poliomyelitis or other virus could be isolated from portions of the brain and cord and histologic examination of the brain showed no lesions suggestive of poliomyelitis.

At least three other fatal illnesses characterized by kidney or central nervous system involvement were brought to the attention of the Evaluation Center, usually reported as poliomyelitis. These were later determined through autopsy and virologic studies not to be poliomyelitis. Since none of these children received injections of either vaccine or placebo, the details of their illnesses are not recorded here.

Review of Massachusetts and Central New York State Experience

In the twenty-five township study areas of Massachusetts and in six central New York State counties the occurrence of a clinical disease simulating poliomyelitis served to complicate vaccine evaluation. For this reason further details are presented here of the experience in each of these districts, which suggest strongly that few of the illnesses encountered there were poliomyelitis as currently defined. It was debated as to whether the experience from Massachusetts and central New York State should be deleted from the combined analyses for placebo areas. It was deemed best to retain them since they represented cases which clinically were called poliomyelitis, and the number falling into critical categories appeared to be so small as not to influence seriously the more significant analyses.

Massachusetts: The total study population of Massachusetts included 14,173 completely vaccinated children, 14,137 who received a complete series of placebo inoculations and 17,565 who were not inoculated.

A total of 44 illnesses reported as poliomyelitis occurred during the period June 26 - December 31, 1954 in this population. Clinically these illnesses resembled poliomyelitis with fever, stiff neck and back. There was an increase in cells in the spinal fluid of all but three of these patients. Based on the initial investigation 38 of the 44, or 86 percent, were reported as non-paralytic. More refined study with muscle gradings at 10-20 and 50-70 days after onset resulted in classification of the reported cases as follows:

Non-paralytic		6
Paralytic-spinal	Grade I	11
	Grade II	13
	Grade III	3
	Grade IV	2
Paralytic-Bulbo-spinal	Grade I	2
	Grade III	1
Not Polio		6

It will be recalled, however, that the classification paralytic grade I refers to patients without muscle score and grade II with scores up to 20. Scores of this magnitude may represent only a small scattering of muscle involvement at the fair level. Furthermore, the physical therapist's pattern of grading in Massachusetts seems to have led to the classification of a number of cases (using the established criteria) as grade II paralytic when in other areas these might have been called grade I. Even then their severity distribution was less than that in the total placebo controls (Table 3a) although quite similar to that in observed controls (3b). Thus, the bulk of disease seen in the study areas of Massachusetts was mild clinically and without extensive paralysis.

The laboratory study by Dr. Enders and his associates of stool specimens from 43 of these patients and paired bloods from 25 served to confirm the suspicion that very few of the illnesses were indeed poliomyelitis. Type III poliomyelitis virus was recovered from three patients and these represented the only isolations. It is interesting to note that two of these patients were the only ones classified as paralytic grade IV and one was bulbo-spinal with a score of 28.

Of the remaining 40 cases where stool was examined so-called orphan, unidentified viruses were recovered from 31. Nine stools were negative. The significance of these orphan viruses as etiologic agents of the clinical disease in question is undetermined. Based on study of paired sera the poliomyelitis antibodies in those patients from whom orphan viruses were recovered fall into the following categories:

Antibody to one type only	1	Serologically positive - Type I - 4/1024
	6	Possible polio 3 had high titers to only Type II 3 had high titers to only Type I
Antibody to several types	8	Indeterminate
No antibodies to any type	3	
Specimens not tested or inadequate	13	

The distribution of the reported cases in vaccinated and placebo groups is as follows:

	Vaccine	Placebo
Paralytic	5	11
Non-Paralytic	2	2
Not Polio	2	-
Cases With Virus Isolated	-	1

Central New York State: In the six counties of central New York State (Cayuga, Jefferson, Oneida, Onondaga, Oswego and Tompkins) the poliomyelitis experience was very similar to that of Massachusetts. The disease in a few other New York study areas showed similar characteristics, but discussion here is limited to the six counties mentioned since the examination of stool and blood samples from patients in these areas was all done in one laboratory. The discussion below follows the same pattern as was presented for the data from Massachusetts.

The total study population of these areas included 16,223 vaccinated children; 16,143 who received placebo; and 20,826 not inoculated.

A total of 60 cases of poliomyelitis was reported during the period June 20 to December 31, 1954. The seasonal pattern of these illnesses as in Massachusetts did not differ from that of the total poliomyelitis case experience. A plateau of incidence occurred between the week of August 7 and September 20. A secondary peak occurred in early October, just as was true of reported poliomyelitis elsewhere in the United States. The secondary attack rate was far higher than that observed in clinical poliomyelitis. Occasionally four cases were reported from the same family.

Clinically, these illnesses were similar to those seen in Massachusetts. Spinal fluid examination was not done in 7 and was negative in 8. Only seven cases (12 percent) would be classified as paralytic based on initial investigation. With the aid of other clinical data and muscle examinations carried out at 10-20 and 50-70 days after onset the following more detailed classification is possible. The shift as compared with the Massachusetts experience of cases from grade II paralytic into the categories non-paralytic and grade I paralytic may be accounted for on the basis of variation in interpretation of the two physical therapists making these examinations.

Non-Paralytic		23
Paralytic	Grade I	17
	Grade II	3
	Grade III	1
	Grade IV	1
Bulbo-Spinal	Grade II	2
	Grade III	2
	Grade IV	1
Not Polio		10

The laboratory studies carried out by Dr. Seymour Kalter and his staff included the examination of stool from 46 and paired bloods from 50 of these patients. Type I poliomyelitis virus was recovered from 8 patients and Type III from one. So-called orphan viruses were recovered from 29 and the remaining 8 were stool negative. The serologic findings in patients with poliomyelitis virus in the stool were not uniformly consistent. In two, a 4-fold or greater rise in homologous antibody was observed. In one, observed homologous antibody alone was shown without rise. In two, a 4-fold or greater rise was observed to more than one type. In two, a 4-fold or greater rise occurred to a heterologous type but not to the type of virus reported from the patient. In one, a 4-fold rise was observed. In two no poliomyelitis antibodies to any type were found and in one the serologic changes were irregularly up and down.

The serologic findings with poliomyelitis virus in the patients found to have "orphan" viruses in the stool were equally difficult to interpret. They fall into the following categories:

Four-fold rise to type I	1
Antibody present to a single type	7
No antibody or present at low level only	12
Antibody to several types	6
Not tested	3

One is confronted with the question of whether these agents are at times coincidental with poliomyelitis virus infection as is true of Coxsackie viruses, and whether their presence excludes the case from consideration as poliomyelitis. There is information from the laboratories that some of the agents originally listed as orphans have by subsequent work been shown to be mixtures with specific poliomyelitis virus.

The distribution of these reported cases in vaccinated and placebo groups is as follows:

	Vaccine	Placebo
Paralytic	6	8
Non-Paralytic	8	5
Not Polio	4	3
Cases With Virus Isolated	2	1

Further clinical, epidemiological and laboratory study of this disease is needed to define its limits and establish its identity and etiology. It seems clear, however, that it was not classical poliomyelitis associated with currently recognized types of virus.

Present information indicates that they are not Coxsackie viruses. Whether they represent another serologic type of poliomyelitis or whether the illness is merely another syndrome which can be confused with mild poliomyelitis is to be learned. It is, however, of interest that a relatively high percentage of patients have high levels of antibody to more than one type of poliomyelitis virus.

Field Trials in Canada and Finland

Because of the production schedule of vaccine during the Spring of 1954, sizeable quantities of vaccine became available after the first and second inoculations had been administered in the study areas of the United States. It was therefore considered feasible to extend the trial to other areas and accordingly the Provinces of Canada were invited to participate. Three areas expressed interest in undertaking studies using placebo controls, according to the established plan. In similar fashion, Finland was enrolled in the study, because epidemiological considerations suggested strongly that a major epidemic of poliomyelitis might be anticipated. The unique characteristics

of each study plan are presented below, followed by a summary of the poliomyelitis experience in these areas, which have been combined because the same lot of vaccine (No. 513) was utilized in all these areas and the total number of cases of poliomyelitis in the test and control groups was small.

1. Province of Manitoba. The study design in Manitoba followed exactly that used in placebo control areas of the United States although only portions of the Province participated. Initial clinics were held June 15, and it was necessary to complete the clinics after schools were closed for the summer. Approximately 63 percent of children in grades 1, 2 and 3, were inoculated:

complete series of vaccine	2973
complete series of placebo	2839
not inoculated	3961

2. Halifax, Nova Scotia. The city of Halifax participated in similar fashion, except that the kindergarten was substituted for the third grade. This was done, because in that area the poliomyelitis attack rate is distinctly higher in five year old children. First clinics were held on June 1 and 58 percent of the children in these grades were inoculated:

complete series of vaccine	1432
complete series of placebo	1433
not inoculated	2179

3. Province of Alberta. In Alberta the Provincial Health authorities found it necessary to offer the opportunity of participation to each of the approximately forty health districts. Since the amount of vaccine available was sufficient for only about one fourth of the children in grades 1, 2 and 3 of the twenty eight districts which signified interest in enrolling in the study, each district medical officer of health was given the responsibility of selecting those schools to be included. In some of the areas the names of only the inoculated children were entered on the Registration Schedule. First clinics were held on June 6 and in the schools selected for study, 66 percent of the children were inoculated:

complete series of vaccine	8051
complete series of placebo	8048
not inoculated	8836

4. Helsinki - Finland. In the city of Helsinki and the surrounding county, the plan of study had to be modified since schools were closed for the summer long before the first clinic was held. It was decided to offer inoculations to any interested children in the age groups five through fourteen years. The administrative problems of this plan necessitated a change in the established procedure of differentiating vaccine and placebo material. The code was simplified so as to refer to one of these substances as "AA" and the other "BB". A total of 20,147 children was inoculated. They were distributed by age as follows:

Under 6 years	3911
6	2874
7	3045
8	3107
9	2042
10 or more	5134
Age unknown	34

First clinics were held on about July 1. Those receiving the complete series of vaccine totaled 9482 compared to 9309 who received the complete series of placebo inoculations.

Occurrence of Poliomyelitis in Vaccinated and Placebo Control Groups: Evaluation of the prophylactic effect of vaccine was severely limited by the small number of cases occurring in these study populations. These numbers are reduced still further when attention is limited to cases with onset two weeks or more after the third series of vaccination clinics. Even though Finland during 1954 experienced its largest poliomyelitis epidemic (a total of 790 cases reported with 603 designated paralytic) only 13 occurred in inoculated children. Of these, 4 received an incomplete series of inoculations and only 7 of those given the complete series had onset more than two weeks after the third clinics were held. The distribution of these cases for Canada and Finland combined by diagnostic category and by vaccination status, is presented in the following table (cases occurring in non-inoculated and partially inoculated children are not listed).

Although the number of cases involved is small, the attack rate per 100,000 population in vaccinated is significantly lower than that in placebo control children ($P = 0.035$) when the Canadian and Finnish experience is combined and consideration limited to cases of paralytic spinal poliomyelitis with a score, plus any other cases from whom poliomyelitis virus was isolated. This subclassification represents an attempt to select those illnesses which are rather firmly established as due to poliomyelitis virus. The two cases in this subclassification with onset prior to two weeks following clinic 3, both received three inoculations of placebo and had onset of symptoms on 7/25 and 8/7 respectively, some days after their third inoculation. It may be considered justifiable, therefore, to make the comparison between seven cases in the placebo control group and the one case in a vaccinated child.

Pre- and post-vaccinal bloods obtained in the three Canadian areas have been studied for evidence of antigenic response following use of vaccine lot No. 513. The response was moderately good, although relatively less to Type I. It should be recalled that Type I virus was the only type recovered from study cases in Canada and Finland.

Poliomyelitis Study Cases by Diagnostic Class and Vaccination Status, for the Study Areas of Canada and Finland

	All Reported Cases With Onset From Date of Clinic No. 1 to December 31		Cases With Onset More Than Two Weeks After Clinic No. 3 to December 31	
	Vaccinated	Placebo	Vaccinated	Placebo
Canada				
Population	12,456	12,320	12,456	12,320
Paralytic				
Spinal - Zero Score	3	1*	2	1*
Spinal - 1+ Score	0	1*	0	1*
Bulbar and Bulbo-Spinal	0	1*	0	0
Non Paralytic	1	2	0	2
Not Polio	2	2	2	1
Total	6	7	4	5
Finland				
Population	9,482	9,309	9,482	9,309
Paralytic				
Spinal - Zero Score	1	0	1	0
Spinal - 1+ Score	1	2	1	2
Bulbar and Bulbo-Spinal	0	2*	0	1*
Non-Paralytic	2	0	1	0
Not Polio	0	1	0	1
Total	4	5	3	4
Canada and Finland Combined				
Total Population	21,938	21,629	21,938	21,629
Total Cases	10	12	7	9
Paralytic With Score +Other cases With Virus Isolated	1	7	1	5
Attack Rate/Per 100,000 Population	4.6	32.4	4.6	23.1

*Type I Virus Isolated.

Study of Family Associates of Poliomyelitis Cases

In addition to the investigation of cases of poliomyelitis in study children, the field trial included the study of all other reported cases of poliomyelitis in the trial areas, when a study child resided in the family. These cases were subjected to clinical and epidemiological review, but for the most part the standard physical therapist examinations and laboratory study of stool and blood samples were not done. This ancillary project had as its objective the determination and comparison of the secondary poliomyelitis attack rate in vaccinated versus control study children, who were exposed to the disease in the household. As part of this phase of the field trial, a number of the participating laboratories, with the help of the local health departments involved, carried on extensive study of all members of these families, with attempts to isolate virus and measure poliomyelitis antibody levels in this population. These observations are not included as a part of this report except where they assist in achieving laboratory confirmation of poliomeylitis infection in a study case. Thus, if the study case failed to show poliomyelitis virus in the stool, but virus was recovered from a family associate, this served as additional evidence to confirm the diagnosis.

Although the mass of accumulated data on family associates has not been fully digested as yet, a few pertinent observations may be made at this time:

Placebo Control Areas: In placebo control areas there were 420 primary index cases in study children and 563 primary index cases in other individuals, where a study child resided in the household. The total population of these households included 5348 persons. When attention is narrowed to the study children (1177) in this entire experience, who were exposed to a reported case of poliomyelitis in the household, the following observations become apparent, after the 420 index cases in study children are deleted:

	Total	Vaccinated	Placebo
Study Children Exposed to Case in Household	477	233	244
Secondary Cases of Polio with Virus Isolated, Occuring During 1 Month After Onset of Index Case	9	1	8
Secondary Attack Rate-Percent	1.89	0.43	3.28

Although these numbers are small, the difference in the secondary attack rate between vaccinated and placebo inoculated children, based on cases confirmed by virus isolation, is statistically significant. The probability of having a divergence this great or greater (in the same direction) approximates 0.022.

Review of the diagnostic classification of these nine secondary cases indicates that the one case occurring in a vaccinated child was paralytic, grade III with Type I virus recovered. From the eight remaining cases, occurring in children receiving placebo, Type I virus was recovered from five and Type III from three. Only one of these illnesses was non-paralytic, the balance being classified as follows:

Paralytic Grade	I - 2
Grade	II - 1
Grade	III - 2
Grade	IV - 1
Grade	V - 1

Thus, in this situation, which approximates an experimental model, a sharp difference in attack rate is observed between those given vaccine and those given placebo. The one apparent failure of vaccine to protect (Type I virus recovered) occurred in Utah where the lot of vaccine used, produced significant antibodies to Type III only.

Observed Control Areas: The same type of family investigation was carried out in the observed control areas. However, it is possible that case reporting in non-inoculated 1st and 3rd grade family associates of index cases was not as complete as was the situation in vaccinated children. Certainly, since the mother, the physician, and the health officer all knew who was vaccinated, the possibility of unconscious bias in diagnosis existed. Furthermore, the clinical and laboratory follow-up of the secondary cases was not so complete as in placebo areas. This consideration plus the complexities of lots of vaccine used, make comparison hazardous.

Despite these inadequacies, however, the data are presented below for consideration. A total of 1712 study children were exposed to a case of poliomyelitis in the household. Of these, 635 represent primary index cases. Of the balance, after these cases are deducted, 251 were vaccinated and 683 were non-vaccinated study children who were members of the 1st or 3rd grade. The secondary attack rates during the month after onset of the index case are as follows:

	Vaccinated	Control 1st & 3rd grade
Study Children Exposed to Case in Household	251	683
Total Reported Cases	5	14
Secondary Attack Rate-%	2.0	2.0
Cases with Virus Isolated	1	6
Secondary Attack Rate-%	0.4	0.9

These data are subject to the limitations mentioned above and do not show a statistically significant difference between the secondary attack rate in vaccinated compared with unvaccinated control children. These findings do not, however, invalidate the more complete and unbiased observations made in placebo control areas.

Administration of Gamma Globulin to Members of the Study Population, May 1, to December 31, 1954

Although it was urged that gamma globulin not be administered to children in the Study Population except for occasional clear cut indications such as in the prophylaxis of measles and hepatitis, it was realized that some record should be kept of its use. Each study area was requested to collect information currently on this matter and report to the Evaluation Center at the end of the year identifying the study child, the date gamma globulin was administered and for what purpose. For the placebo control areas nearly equal numbers of vaccinated and placebo inoculated children received gamma globulin, 0.9% and 1.1% respectively. Half of the gamma globulin used was for associates of poliomyelitis, a third for measles prophylaxis given largely during May, June and July and the balance for infectious hepatitis, scattered throughout the summer. There was no group use of the material for poliomyelitis prophylaxis.

In similar fashion for observed control areas 0.4% of vaccinated children were reported to have received gamma globulin during the study period compared to 0.4% of the control children. In contrast to the experience in the placebo control areas the great bulk of the gamma globulin administered was in terms of group prophylaxis for poliomyelitis (49.6% of all gamma globulin used). Practically all of that given to vaccinated children was administered in October. It is interesting that a similar percentage of vaccinated and non-vaccinated children were reported to have received gamma globulin group prophylaxis (0.2%). On the other hand the use of gamma globulin in contacts of poliomyelitis cases was much more frequent in non-vaccinated than in vaccinated children, 0.2% compared to 0.08%.

Obviously, no matter what one believes about the effectiveness of gamma globulin in preventing poliomyelitis the total use of this material and its equal distribution in vaccinated and non-vaccinated children indicates that it did not interfere with proper evaluation of the effectiveness of vaccine.